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ARTICLES

15 A Cluster of *Escherichia coli* O157:H7 Infections With the Hemolytic-Uremic Syndrome and Death in California—A Mandate for Improved Surveillance
A M SHEFER, D KOO, S B WERNER, E D MINTZ, R BARON, J G WELLS, T J BARRETT, M GINSBERG, R BRYANT, S ABBOTT, and P M GRIFFIN

20 Pediatric Hospital Admissions for Measles—Lessons From the 1990 Epidemic
G F CHAVEZ and A A ELLIS

26 Patient Preferences for Management of Localized Prostate Cancer
D J MAZUR and D H HICKAM

31 Substance-Impaired Physicians—Probationary and Voluntary Treatment Programs Compared
H D NELSON, A M MATTHEWS, D E GIRARD, and J D BLOOM

37 Western Impressions of the Hong Kong Health Care System
C L BENNETT, G K PEI, and J E ULTMANN

CONFERENCES AND REVIEWS

43 Cervical Spondylosis—An Update
B M McCORMACK and P R WEINSTEIN

EPITOMES

52 Important Advances in Radiology

ALERTS, NOTICES, AND CASE REPORTS

61 Tension Pneumoperitoneum
S Y CHAN, C M KIRSCH, W A JENSEN, and J SHERCK

64 Wegener's Granulomatosis Presenting As Dilated Cardiomyopathy
J D DAY, K E ELLISON, I SCHNITTGER, and M G PERLROTH

TOPICS IN PRIMARY CARE MEDICINE

67 Prophylaxis Against Opportunistic Infections in Patients Infected With the Human Immunodeficiency Virus
L W CHEEVER, R E CHAISSON, and J E GALLANT

EDITORIALS

80 California's 1988-1991 Measles Epidemic—The Last One?
N J SMITH, L G DALES, and S H WATERMAN

81 Progress in Treatments for Substance-Impaired Physicians
J H SHORE

COMMENTARY

74 Caution: The Meter Is Running—Informing Patients About Health Care Costs
M S WILKES and D L SCHRIGER

CORRESPONDENCE

83 Genetics and Homosexuality

LESSONS FROM THE PRACTICE

84 Mrs O'Brien's Story
G S REITER

85 Gloria! . . . Glooooria!
E B OPPENHEIM

86 Courage
ANONYMOUS

OTHER FEATURES

10 Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming

14 In Memoriam

87 Instructions for Authors

90 Classified Advertising

96 Western State Medical Associations' Meetings

Detailed Table of Contents: 4, 6, 8, 9

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References: 1. Neu HC, Wilson APR, Grüneberg RN: Amoxycillin/clavulanic acid: a review of its efficacy in over 38,500 patients from 1979 to 1992. *J Chemother* 1993;5(2):67-93. **2.** *Clinical Efficacy Update I-III,* 1995, SmithKline Beecham Pharmaceuticals.

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Bacteriological studies to determine the causative organisms and their susceptibility to *Augmentin* should be performed together with any indicated surgical procedures Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above Once results are known, adjust therapy, if appropriate
CONTRAINDICATIONS: Patients with a history of allergic reactions to any penicillin, or patients with a history of *Augmentin*-associated cholestatic jaundice/hepatic dysfunction
WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS BEFORE INITIATING THERAPY WITH *AUGMENTIN*, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.** Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic associated colitis " After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis Use *Augmentin* cautiously in patients with evidence of hepatic dysfunction Hepatic toxicity associated with *Augmentin* use is usually reversible On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide) These have generally been cases associated with serious underlying diseases or concomitant medications (See CONTRAINDICATIONS and ADVERSE REACTIONS.)
PRECAUTIONS: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.
A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted
Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin Co-administration of probenecid cannot be recommended The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients There are no data with *Augmentin* and allopurinol administered concurrently
Drug/Laboratory Test Interactions: Oral administration of *Augmentin* will result in high urine concentrations of amoxicillin High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin and therefore *Augmentin*, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Tes-Tape®) be used
Following administration of ampicillin to pregnant women a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone and estradiol has been noted This effect may also occur with amoxicillin and therefore *Augmentin*.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential **Mutagenesis:** The mutagenic potential of *Augmentin* was investigated *in vitro* with an Ames test, a human lymphocyte cytogenetic assay, a yeast test and a mouse lymphoma forward mutation assay, and *in vivo* with mouse micronucleus tests and a dominant lethal test All were negative apart from the *in vitro* mouse lymphoma assay where weak activity was found at very high, cytotoxic concentrations
Impairment of Fertility: *Augmentin* at oral doses of up to 1200 mg/kg/day (5 7 times the maximum human dose, 1480 mg/m²/day, based on body surface area) was found to have no effect on fertility and reproductive performance in rats dosed with a 2 1 ratio formulation of amoxicillin clavulanate
Teratogenic effects: Pregnancy (Category B): Reproduction studies performed in pregnant rats and mice given *Augmentin* at oral dosages up to 1200 mg/kg/day, equivalent to 7200 and 4080 mg/m²/day, respectively (4 9 and 2 8 times the maximum human oral dose based on body surface area), revealed no evidence of harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed
Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary
Nursing Mothers: Ampicillin class antibiotics are excreted in the milk, therefore, caution should be exercised when *Augmentin* is administered to a nursing woman
ADVERSE REACTIONS: *Augmentin* is generally well tolerated The majority of side effects observed in clinical trials were mild and transient, <3% of patients discontinued therapy because of drug-related side effects The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose Other less frequently reported reactions include: abdominal discomfort, flatulence and headache
The following adverse reactions have been reported for ampicillin class antibiotics
Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis, mucocutaneous candidiasis and pseudomembranous colitis Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS) Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome) and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis) These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See WARNINGS) A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin* The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued The hepatic dysfunction, which may be severe, is usually reversible On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications Interstitial nephritis and hematuria have been reported rarely Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin* Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely
DOSAGE AND ADMINISTRATION
Since both the *Augmentin* 250 mg and 500 mg tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), 2 *Augmentin* 250 mg tablets are not equivalent to 1 *Augmentin* 500 mg tablet. Therefore, 2 *Augmentin* 250 mg tablets should not be substituted for 1 *Augmentin* 500 mg tablet.
Dosage:
Adults: The usual adult dose is 1 *Augmentin* 500 mg tablet every 12 hours or 1 *Augmentin* 250 mg tablet every 8 hours For more severe infections and infections of the respiratory tract, the dose should be 1 *Augmentin* 875 mg tablet every 12 hours or 1 *Augmentin* 500 mg tablet every 8 hours
Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe Severely impaired patients with a glomerular filtration rate of <30 mL/minute should not receive the 875 mg tablet Patients with a glomerular filtration rate of 10 to 30 mL/minute should receive 500 mg or 250 mg every 12 hours, depending on the severity of the infection Patients with a less than 10 mL/minute glomerular filtration rate should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection
Hemodialysis patients should receive 500 mg or 250 mg every 24 hours They should receive an additional dose both during and at the end of dialysis
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals (See WARNINGS)
Pediatric Patients: Pediatric patients weighing 40 kg or more should be dosed according to the adult recommendations
Due to the different amoxicillin to clavulanic acid ratios in the *Augmentin* 250 mg tablet (250/125) versus the *Augmentin* 250 mg chewable tablet (250/62.5), the *Augmentin* 250 mg tablet should not be used until the pediatric patient weighs at least 40 kg or more.
Administration: *Augmentin* may be taken without regard to meals, however, absorption of clavulanate potassium is enhanced when *Augmentin* is administered at the start of a meal To minimize the potential for gastrointestinal intolerance, *Augmentin* should be taken at the start of a meal
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(Chavez GF, Ellis AA: Pediatric hospital admissions for measles—Lessons from the 1990 Epidemic. West J Med 1996; 165:20-25)

To examine the descriptive epidemiology of serious measles complications and associated hospital costs during a major epidemic, we used California population-based hospital discharge data to identify hospital admissions for measles during 1986 through 1990 (ICD-9 code 055, n = 4,201). We examined 5-year trends and, for 1990 pediatric epidemic cases (n = 2,234), sociodemographic and hospital admission financial data. Hospital admission rates for measles rose significantly between 1986 and 1990. During the 1990 epidemic, preschool children aged 1 to 5 years, Medi-Cal beneficiaries, Hispanics, and those living in urban counties accounted for most hospital admissions. Young infants and residents of southern California and the San Joaquin Valley had the highest risks. Medi-Cal beneficiaries and Asian children were at an increased risk for death during the hospital stay. The average hospital admission cost was $8,201, and the average length of hospital stay was 4.6 days. Hospital costs amounted to $18 million, two thirds of which was paid for by Medi-Cal. Measles is a serious disease that can result in severe complications requiring lengthy and costly hospital stays. We must remain alert to its continuing threat, complications, and resulting financial burdens.

MEASLES **PEDIATRIC HOSPITAL ADMISSIONS**

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The Western Journal of Medicine

VOLUME 165 • NUMBERS 1/2 • JULY/AUGUST 1996

CONTENTS

ARTICLES

15 **A Cluster of *Escherichia coli* O157:H7 Infections With the Hemolytic-Uremic Syndrome and Death in California—A Mandate for Improved Surveillance**

ABIGAIL M. SHEFER, MD; DENISE KOO, MD; S. BENSON WERNER, MD; ERIC D. MINTZ, MD; ROY BARON, MD; JOY G. WELLS, PhD; TIMOTHY J. BARRETT, PhD; MICHELE GINSBERG, MD; RAY BRYANT, PhD; SHARON ABBOTT, PhD; and PATRICIA M. GRIFFIN, MD

From the Division of Field Epidemiology, Epidemiology Program Office, and the Foodborne and Diarrheal Diseases Branch, Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; the Division of Communicable Disease Control, California Department of Health Services, Berkeley, California; and the San Diego Department of Health Services, San Diego, California.

20 **Pediatric Hospital Admissions for Measles—Lessons From the 1990 Epidemic**

GILBERTO F. CHAVEZ, MD, MPH, and ARTHUR A. ELLIS, MA

From the Maternal and Child Health Branch, California Department of Health Services, Sacramento, and the Pregnancy and Infant Health Branch, Division of Reproductive Health, National Center for Health Promotion and Chronic Disease Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia.

26 **Patient Preferences for Management of Localized Prostate Cancer**

DENNIS J. MAZUR, MD, PhD, and DAVID H. HICKAM, MD, MPH

From the Medical Service and Health Services Research and Development, Department of Veteran Affairs Medical Center, Portland, Oregon.

31 **Substance-Impaired Physicians—Probationary and Voluntary Treatment Programs Compared**

HEIDI D. NELSON, MD, MPH; ANNETTE M. MATTHEWS; DONALD E. GIRARD, MD; and JOSEPH D. BLOOM, MD

From the Department of Medicine, the Biomedical Information Communication Center, and the Office of the Dean of the School of Medicine, Oregon Health Sciences University, and the Veterans Affairs Medical Center, Portland.

37 **Western Impressions of the Hong Kong Health Care System**

CHARLES L. BENNETT, MD, PhD; GLORIA K. PEI, MD; and JOHN E. ULTMANN, MD

From the Department of Health Services Research, the Lakeside Veterans Affairs Medical Center, and the Division of Hematology/Oncology, Northwestern University, Chicago, Illinois; the Department of Community Medicine and Unit for Behavioural Sciences, University of Hong Kong; and the Section of Hematology/Oncology, the Department of Medicine, and the Cancer Research Center of the University of Chicago.

CONFERENCES AND REVIEWS

43 **Cervical Spondylosis—An Update**

BRUCE M. McCORMACK, MD, and PHILLIP R. WEINSTEIN, MD

From the Department of Neurological Surgery, University of California, San Francisco, School of Medicine, and the Veterans Affairs Medical Center, San Francisco.

(Continued on Page 6)

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Propylthiouracil-Induced Hepatotoxicity

Editorials, Commentary, Lessons From the Practice

(Continued from Page 4)

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Radiology

Items of progress in radiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

52 **Percutaneous Core Biopsy of the Breast**
WILLIAM BRANT, MD

53 **Current Status of Thrombolysis**
JAMES J. SELL, MD; FREDERICK W. RUPP, MD; and ROBERT J. TELEPAK, MD

53 **Magnetic Resonance Imaging, Positron Emission Tomography, and Single-Photon-Emission Computed Tomography in Epilepsy**
BRIAN W. CHONG, MD, and DAVID K. SHELTON, MD

54 **Imaging of Appendicitis**
REBECCA HULETT, MD

55 **Spiral and Ultrafast Computed Tomography for Noninvasive Cardiac Imaging in Children**
SJIRK J. WESTRA, MD

56 **Doppler Ultrasonography of Transjugular Intrahepatic Portosystemic Shunts**
VICKIE A. FELDSTEIN, MD, and MAITRAY D. PATEL, MD

57 **Spiral Computed Tomography and Magnetic Resonance Imaging in the Detection of Pulmonary Emboli**
MARK BALDECK, DDS, MD, and LOREN KETAI, MD

58 **Magnetic Resonance Imaging of Radiographically Occult Bony Trauma**
MARK ANDERSON, MD

58 **Magnetic Resonance Imaging of the Breast**
ROBERT ROSENBERG, MD; LAURENCE D. CAMBRON, PhD, MD; and MICHAEL R. WILLIAMSON, MD

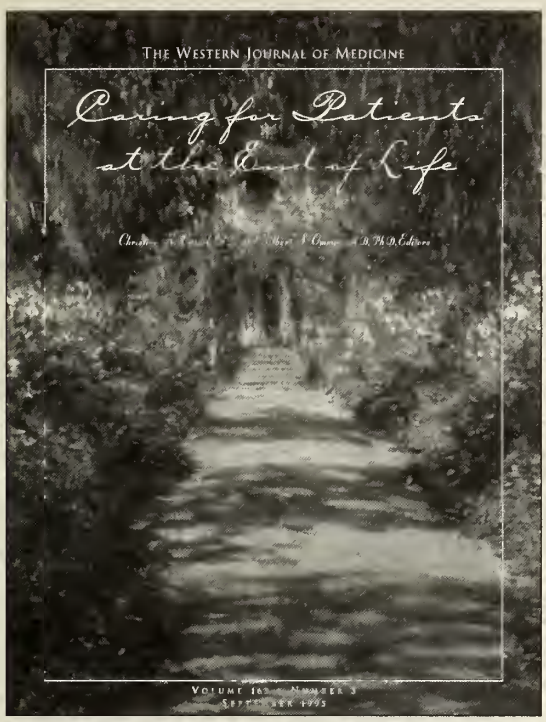
59 **Radiosurgery**
DAVID A. LARSON, PhD, MD, and MICHAEL W. McDERMOTT, MD

ALERTS, NOTICES, AND CASE REPORTS

61 **Tension Pneumoperitoneum**
STEPHANIE Y. CHAN, MD; CARL M. KIRSCH, MD; WILLIAM A. JENSEN, MD; and JOHN SHERCK, MD
From the Departments of Medicine and Surgery, Santa Clara Valley Medical Center, San Jose, California.

64 **Wegener's Granulomatosis Presenting as Dilated Cardiomyopathy**
JOHN D. DAY, MD; KRISTIN E. ELLISON, MD; INGELA SCHNITTGER, MD; and MARK G. PERLROTH, MD
From the Division of Cardiology, Department of Medicine, Stanford University Medical Center, Stanford, California.

(Continued on Page 8)



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Special Issue Editors, 1995

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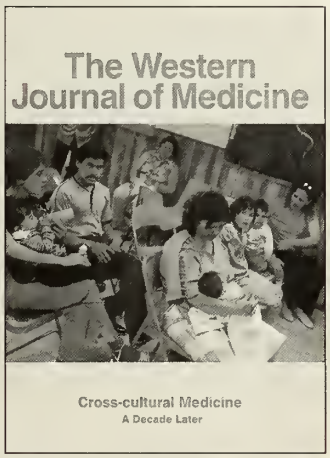

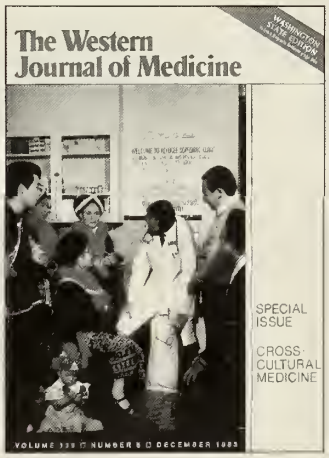

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(Continued from Page 6)

TOPICS IN PRIMARY CARE MEDICINE

67 **Prophylaxis Against Opportunistic Infections in Patients Infected With the Human Immunodeficiency Virus**

LAURA W. CHEEVER, MD; RICHARD E. CHAISSON, MD; and JOEL E. GALLANT, MD, MPH

From the Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland.

COMMENTARY

74 **Caution: The Meter Is Running—Informing Patients About Health Care Costs**

MICHAEL S. WILKES, MD, PhD, and DAVID L. SCHRIGER, MD, MPH

From the Division of General Internal Medicine and Health Services Research, Department of Medicine, and the Emergency Medicine Center, University of California, Los Angeles, School of Medicine.

EDITORIALS

80 **California's 1988-1991 Measles Epidemic—The Last One?**

NATALIE J. SMITH, MD, MPH; LORING G. DALES, MD, MPH; and STEPHEN H. WATERMAN, MD, MPH

From the Division of Communicable Disease Control, California Department of Health Services, Berkeley, California.

81 **Progress in Treatments for Substance-Impaired Physicians**

JAMES H. SHORE, MD

From the Colorado Psychiatric Hospital, University of Colorado Health Sciences Center, Denver.

CORRESPONDENCE

83 **Genetics and Homosexuality**

LINDA H. MORSE, MD

VICTOR I. REUS, MD, Responds

LESSONS FROM THE PRACTICE

84 **Mrs O'Brien's Story**

GARY S. REITER, MD

Dr Reiter is in private practice in Holyoke, Massachusetts.

85 **Gloria! . . . Glooooria!**

ELLIOTT B. OPPENHEIM, MD, JD, LLM

Dr Oppenheim practiced family medicine before becoming a medical-legal consultant.

86 **Courage**

ANONYMOUS

(Continued on Page 9)

(Continued from Page 8)

OTHER FEATURES

10 **Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming**

14 **In Memoriam**

87 **Instructions for Authors**

90 **Classified Advertising**

96 **Western State Medical Associations' Meetings**

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

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The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

October 7-10—**Visiting Fellowships in MRI.** University of Arizona College of Medicine at the Biltmore Advanced Imaging Center, Phoenix. Mon-Thurs. Contact: (800) 848-4920, ext 2575.

October 14-18—**Neuroradiology: Review and Update.** University of Arizona College of Medicine at the Biltmore Advanced Imaging Center, Phoenix. Mon-Fri. Contact: (800) 848-4920, ext 2575.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

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This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

November 8-10—**8th Annual Anesthesiology Update:1996.** UCD at Monterey Plaza Hotel, Monterey. 14 hrs. $350. Contact: UCD.

January 8-11—**Anesthesiology Update 1997.** UCSD at Hotel del Coronado, Coronado. Wed-Sat. 21 hrs. $375. Contact: UCSD.

January 31-February 2—**35th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Los Angeles at Sheraton Universal Hotel, Universal City. 15 hrs. $295. Contact: David J. Stewart, MB, Prog. Dir., Pediatric Anesthesiology Conf., Children's Hospital Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

CARDIOLOGY

September 26-28—**10th Annual International Workshop on Future Directions in Interventional Cardiology.** American College of Cardiology at Santa Barbara. Thurs-Sat. Contact: ACC, (800) 253-4636, ext 695.

October 3-6—**Coronary Interventions: 1996.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sun. 28 hrs. Contact: Scripps Clinic, (619) 554-8556.

October 10-12—**Cardiology Update 1996.** American College of Cardiology at Carmel Valley Ranch Resort. Thurs-Sat. 12 hrs. Contact: Registration Secretary, Extramural Programs Dept, ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814. (800) 253-4636.

October 17-19—**15th Annual Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 17 hrs. $475. Contact: UCSF.

November 2—**Update in Electrocardiography and Arrhythmias.** UCSF at AHA Hotel, San Francisco. Sat. 7.5 hrs. $175. Contact: UCSF.

November 22-24—**Coronary Heart Disease Update.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sun. 11 hrs. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4569. (800) 421-3756.

December 13-15—**14th Annual Advances in Heart Disease.** American College of Cardiology at San Francisco. Contact: ACC, (800) 253-4636, ext 695.

January 24-26—**Clinical Nuclear Cardiology: Case Review With the Experts.** American College of Cardiology at Los Angeles. Fri-Sun. Contact: ACC, (800) 253-4636, ext 695.

DERMATOLOGY

October 5-9—**11th Combined Skin Pathology Course and Workshop in Dermatopathology.** UCSD at San Diego Princess. Sat-Wed. 37 hrs. $600. Contact: UCSD.

October 17-20—**Minimally Invasive Techniques for Facial Rejuvenation.** UCSF at Embarcadero Hyatt Regency Hotel, San Francisco. Thurs-Sun. Contact: UCSF.

November 2-3—**The Skin From A to Z: Tips on Practical Therapy and Office Techniques.** UCSF. Sat-Sun. Contact: UCSF.

January 31-February 2—**Primary Care Dermatology.** UCSD at San Diego Hilton Beach and Tennis Resort. Fri-Sun. Contact: UCSD.

EMERGENCY MEDICINE

October 17-19—**15th Annual Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 17 hrs. $475. Contact: UCSF.

October 18-20—**The Comprehensive Review in Emergency Medicine and Urgent Care.** Continuing Medical Education Associates at Hyatt Regency, La Jolla. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

October 20-23—**Cellular Injury and Brain Edema, 1996.** Foundation for Pediatric and Laser Neurosurgery, Inc, at Hyatt Regency Hotel, San Diego. Sun-Wed. 19 hrs. $350-$400. Contact: Hector E. James, MD, Coordinator, Foundation for Pediatric and Laser Neurosurgery, Inc, 7930 Frost St, Ste 304, San Diego 92123. (619) 560-4791.

October 21-25—**Emergency Medicine Symposium I.** UCSD. Mon-Fri. 32 hrs. $495. Contact: UCSD.

October 28-November 1—**25th Annual Topics in Emergency Medicine.** UCSF at Holiday Inn, Union Square, San Francisco. Mon-Fri. 32 hrs. $655. Contact: UCSF.

November 11-15—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $495. Contact: UCSD.

December 7-8—**Stabilization and Management of the Critically Ill Child.** UCSF at Mark Hopkins Hotel, San Francisco. Sat-Sun. Contact: UCSF.

December 16-20—**Emergency Medicine Symposium II.** UCSD. Mon-Fri. 32 hrs. $495. Contact: UCSD.

February 17-21— Emergency Medicine Symposium I. UCSD at San Diego Hilton Beach and Tennis Resort. 32 hrs. $495. Contact: UCSD.

(Continued on Page 11)

(Continued from Page 10)

FAMILY PRACTICE/PRIMARY CARE

September 19—**Immunization Update 1966**. CDC Public Health Training Network at local hospitals. Thurs. 3 hrs. Contact: Provider Relations or Education office at your hospital, local health department's Immunization Coordinator or CHDP Program, (619) 594-2115.

September 28—**Stroke Prevention Management in the Primary Care Setting; Update 1966.** UCSF at AHA Hotel, San Francisco. Sat. 7.5 hrs. $160. Contact: Mary Henderson, UCSF Mt Zion Center on Aging, (415) 750-5342.

October 9-11—**Primary Care Medicine: Principles and Practice**. UCSF at AHA Hotel, San Francisco. Wed-Fri. 20 hrs. $525. Contact: UCSF.

October 9-12—**Semiannual Wound Management Workshop: For Primary Care Professionals.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sat. 17 hrs. $475. Contact: UCSD, Edith Bookstein, (619) 454-3212.

October 17-20—**Office Based Orthopaedics for the Primary Care Physician**. UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sun. 18.5 hrs. $395-$450. Contact: UCSF.

October 19—**Symposium on Women's Health**. UCD at UCD Medical Center, Sacramento. Sat. 7 hrs. $70. Contact: UCD.

October 21—**OB/GYN Pathology**. USC at Red Lion Hotel, Glendale. Mon. 8 hrs. $185. Contact: USC.

October 21-23—**Neurology and Outpatient Psychiatry in Primary Care.** Continuing Medical Education Associates at Hyatt Regency, San Diego. 20 hrs, $450. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

November 15-17—**Women's Health Issues in Primary Care**. UCSD at Hilton Hotel, San Diego. Fri-Sun. 17.5 hrs. Contact: UCSD.

November 17-19—**3rd Annual Western Retreat: Practical Primary Care**. Scripps Clinic and Research Foundation at Silverado, Napa. Sun-Tues. 12 hrs. Contact: Scripps, (619) 554-8556.

December 5-6—**Controversies in Women's Health**. UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Fri. 13 hrs. $355. Contact: UCSF.

December 7-8—**Stabilization and Management of the Critically Ill Child**. UCSF at Mark Hopkins Hotel, San Francisco. Sat-Sun. Contact: UCSF.

January 17-19—**Practical Dermatology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego 92198. (800) 993-1632 or (619) 674-5200.

January 20-22—**Ophthalmology and ENT for the Primary Care Physician**. Continuing Medical Education Associates at Hyatt Regency, La Jolla. Mon-Wed. 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego 92198. (800) 993-2632 or (619) 674-5200.

January 31-February 2—**Primary Care Dermatology**. UCSD at San Diego Hilton Beach and Tennis Resort. Fri-Sun. Contact: UCSD.

February 14-16—**Office Gynecology and Women's Health for the Primary Care Physician.** CMEA at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $475. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego 92198. (800) 993-2632 or (619) 674-5200.

February 17-19—**Pediatrics Update 1997**. CMEA at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $475. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego 92198. (800) 993-2632 or (619) 674-5200.

February 17-19—**Clinical Hematology and Oncology: 1997**. Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Scripps, (619) 554-8556.

INFECTIOUS DISEASE

October 26-November 2—**National Infectious Disease Update Conference.** Santa Rosa Kaiser Permanente Medical Center on the Sun Princess Cruise, Western Caribbean. Sat-Fri. 7 hrs, $50-$100. Contact: Infectious Disease Update/SRO, Kaiser Permanente Medical Center, 401 Bicentennial Way, Santa Rosa 95403-2192.

December 5-7—**Clinical Care of the AIDS Patient.** UCSF at Sheraton Place Hotel, San Francisco. Thurs-Sat. 24 hrs. $395. Contact: UCSF.

February 6-8—**Epidemiology and Prevention of Infectious Diseases.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

INTERNAL MEDICINE

September 19-21—**Rheumatology Board Review.** UCSF at Miyako Hotel, San Francisco. Thurs-Sat. 24 hrs. Contact: UCSF.

September 27-October 2—**Internal Medicine 1996—Fall Program.** Continuing Medical Education Associates at Loews Coronado Bay Resort, San Diego. Fri-Wed. $450. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

September 30-October 4—**Texas Internal Medicine Conference**. UCSD at Westgate Hotel, San Diego. Mon-Fri. Contact: UCSD.

October 3-4—**Design and Methods of Clinical Trials.** UCSF at Holiday Inn, Union Square, San Francisco. Thurs-Fri. 12.5 hrs, $285-$375. Contact: UCSF.

December 8—**Endocrine Tumors: 101st Semi-Annual Cancer Seminar**. California Tumor Tissue Registry at Ritz-Carlton Hotel, San Francisco. Sun. 8 hrs. $265. Contact: CTTR, (909) 824-4788.

February 12-14—**Recent Advances in Neurology**. UCSF at Hyatt Regency Hotel, San Francisco. Wed-Fri. 15 hrs. Contact: UCSF.

February 17-20—**Clinical Hematology and Oncology: 1997.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Scripps, (619) 554-8556.

OCCUPATIONAL MEDICINE

October 21-25—**Occupational and Environmental Medicine II**. UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $725. Contact: UCSF.

December 5-6—**Occupational Disorders of the Upper Extremities.** UC Berkeley at San Francisco Airport Hilton Hotel. Thurs-Fri. Contact: UC Berkeley.

ONCOLOGY

October 10-12—**20th Annual Physicians Cancer Symposium.** Scripps-Health at Sheraton Harbor Island Hotel, San Diego. Thurs-Sat. 17 hrs, $425-$450. Contact: Stevens Cancer Center, Scripps Memorial Hospital, PO Box 28, La Jolla 92038-0028; Ruthanne Crawford, (619) 626-6794.

October 19—**15th Annual Cancer Memorial Symposium—Winning Strategy Against Cancer.** Victor Valley Community Hospital at Holiday Inn, Victorville. Sat. 8 hrs, $90. Contact: Hi Desert Joint Cancer Program, Alice Williams, CTR Victor Valley Community Hospital, 15248 11th St, Victorville 92392. (619) 245-8691, ext 3432.

February 17-20—**Clinical Hematology and Oncology: 1997.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Scripps, (619) 554-8556.

(Continued on Page 12)

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
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UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

(Continued from Page 11)

OTOLARYNGOLOGY

September 14-18—**Temporal Bone Surgical Dissection Courses**. The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, (213) 483-4431, ext 7079.

October 17-20—**Minimally Invasive Techniques for Facial Rejuvenation.** UCSF at Embarcadero Hyatt Regency Hotel, San Francisco. Thurs-Sun. Contact: UCSF.

October 19-23—**Temporal Bone Surgical Dissection Courses.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, (213) 483-4431, ext 7079.

October 31-November 1—**Facial Plating in Craniomaxillary Surgery.** UCD at Hyatt Regency Hotel, Sacramento. Thurs-Fri. 13 hrs. $150. Contact: UCD.

November 7-9— **Otolaryngology Update: 1996.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. 18.5 hrs, $425. Contact: UCSF.

November 9-13—**Temporal Bone Surgical Dissection Courses.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, (213) 483-4431, ext 7079

December 7-11—**Temporal Bone Surgical Dissection Courses**. The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, (213) 483-4431, ext 7079.

January 4-8—**Temporal Bone Surgical Dissection Course.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, 2100 W Third St, Los Angeles 90057. (213) 483-4431, ext 7079.

February 1-5—**Temporal Bone Surgical Dissection Course**. The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs. $1,300. Contact: House Ear Institute, (213) 483-4431, ext 7079.

PEDIATRICS

November 9—**Pediatric Pain Management in Managed Care Environment**. Children's Hospital and Health Center at Corning Labs Conference Center, San Diego. Sat. 7 hrs, $85. Contact: Children's Hospital, Continuing Medical Education, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

December 7—**Fifteenth Annual Binational Pediatric Conference.** Children's Hospital and Health Center at Mercy Hospital Education Center, San Diego. Saturday. 5 hrs, $45. Contact: Children's Hospital, Continuing Medical Education, 3020 Children's Way (5021), San Diego, 92123. (619) 576-4072.

December 7-8—**Stabilization and Management of the Critically Ill Child**. UCSF at Mark Hopkins Hotel, San Francisco. Sat-Sun. Contact: UCSF.

January 15-18—**San Diego Cerebral Palsy Symposium.** Children's Hospital at San Diego Marriott Mission Valley. Wed-Sat. 21.5 hrs, $450-$495. Contact: Continuing Medical Education, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

January 27-31— **San Diego Conference on Responding to Child Maltreatment.** Children's Hospital at Town and Country Hotel, San Diego. Mon-Fri. 30.5 hrs, $435. Contact: Registration Coordinator, Center for Child Protection, 3020 Children's Way (MC5016), San Diego 92123. (619) 495-4940.

January 31-February 2—**35th Clinical Conference in Pediatric Anesthesiology**. Children's Hospital Los Angeles at Sheraton Universal Hotel, Universal City. 15 hrs. $295. Contact: David J. Stewart, MB, Program Dir, Pediatric Anesthesiology Conf., Children's Hospital Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

February 28-March 2—**Current Concepts in Pediatric Medicine—10th Anniversary**. Children's Hospital and Health Center at San Diego Hilton Beach and Tennis Resort. Fri-Sun. 16 hrs. $365. Contact: Children's Hospital, CME, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

PLASTIC SURGERY

October 12-13—**New Directions in Lasers and Cosmetic Surgical Procedures**. UCD. Sat-Sun. 13 hrs. $750. Contact: UCD

October 17-20—**Minimally Invasive Techniques for Facial Rejuvenation.** UCSF at Embarcadero Hyatt Regency Hotel, San Francisco. Thurs-Sun. Contact: UCSF.

PSYCHIATRY AND NEUROLOGY

October 11-13—**California Psychiatric Association Annual Meeting**. Rancho Las Palmas Resort. Fri-Sun. 18.5 hrs. Contact: CPA, (800) 772-4271.

November 2-3—**Neurology Update.** UCSD at Hotel del Coronado, Coronado. Sat-Sun. 12 hrs, $350. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

November 8-10—**The 42nd Annual Group Therapy Symposium.** UCSF at Mark Hopkins Hotel, San Francisco. Fri-Sun. Contact: UCSF.

February 12-14—**Recent Advances in Neurology.** UCSF at Hyatt Regency Hotel, San Francisco. Wed-Fri. 15 hrs. Contact: UCSF.

RADIOLOGY

September 28-29—**Ultrasound Update: 1996**. UCD at Red Lion Inn, Sacramento. Sat-Sun. 10 hrs. $190. Contact: UCD.

October 24-25—**Neuroradiology Comprehensive Review.** UCSD at Hotel del Coronado, Coronado. Thurs-Fri. 25 hrs, $550. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

October 26-27—**16th Annual Comprehensive Review of Vascular & Interventional Radiology.** UCSD at Hotel del Coronado, Coronado. Sat-Sun. 14 hrs, $375. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

October 28-November 1—**21st Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, Coronado. Mon-Fri. 27 hrs, $575. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

SURGERY

September 19-21—**Working Together for Success in a Changing Health Environment.** California Thoracic Society at Marriott Hotel, Newport Beach. Thurs-Sat. 10 hrs. Contact: CTS, 202 Fashion Lane, #219, Tustin 92680. (714) 730-1944.

October 31-November 1—**Facial Plating in Craniomaxillary Surgery.** UCD at Hyatt Regency Hotel, Sacramento. Thurs-Fri. 13 hrs. $150. Contact: UCD.

January 4-8—**Temporal Bone Surgical Dissection Course.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, 2100 W Third St, Los Angeles 90057. (213) 483-4431, ext 7079.

UROLOGY

October 5-9—**11th Combined Skin Pathlogy Course & Workshop in Dermatopathology**. UCSD at San Diego Princess. Sat-Wed. 37 hrs, $600. Contact: UCSD.

November 3-7—**VII World Meeting on Impotence.** American Urological Association and UCSF at Sheraton Palace, San Francisco. Mon-Thurs. $400-$475. Contact: UCSF.

GENERAL/MULTIDISCIPLINARY

September 12 and 19—**Arrhythmia Recognition.** American Heart Association at San Leandro. Thurs. 10 hrs, $120. Contact: CPR Seminars, (510) 632-6135.

September 16, 18, 24, 26—**CLS Provider Training.** American Heart Association at San Leandro. Mon and Wed, Tues and Thurs. 16 hrs, $170. Contact: CPR Seminars, (510) 632-6135.

September 21—**Update in Medicine**. USC at San Diego Marriott. Sat. 6 hrs. $75. Contact: USC.

October 18—**ACLS Recertification.** American Heart Association at San Francisco. Fri. 6 hrs, $100. Contact: CPR Seminars, (510) 632-6135.

(Continued on Page 13)

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October 19-20—**ACLS Provider.** American Heart Association at San Francisco. Sat-Sun. 16 hrs, $170. Contact: CPR Seminars, (510) 632-6135.

October 29-31—**ABC's Second Annual Telemedicine and Telehealth Conference.** UCD at Anaheim Convention Center. Tues-Thurs. $450-$550. Contact: UCD, (800) 829-3400.

November 8—**Assault Prevention for the Healthcare Provider**. CPR Seminars at San Leandro. Fri. 5 hrs. $96. Contact: CPR Seminars, (510) 632-6135.

December 12-14—**Diagnosis and Treatment of Back Pain—The Next Level.** St Mary's Hospital at Stanford Court Hotel, San Francisco. Thurs-Sat. Contact: Aubrey A. Swartz, MD, American Back Society, St Joseph's Professional Center, 2647 E 14th St, Ste 401, Oakland 94601. (510) 536-9929.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

September 18-21—**Enhancing Quality and Value in Cardiovascular Care.** University of Colorado Health Sciences Center at Vail. Thurs-Sat. Contact: U of Colo.

October 28-November 1—**42nd Annual Family Practice Review (Repeat of June program).** University of Colorado Health Sciences Center at Denver. Mon-Fri. Contact: U of Colo.

December 6-7—**5th Update in Infectious Disease: Bugs and Drugs in the '90s.** University of Colorado Health Sciences Center at Denver. Fri-Sat. Contact: U of Colo.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

September 7-8—**New Mexico Chapter-American College of Surgeons Annual Meeting.** Inn of the Mountain Gods, Ruidoso. Sat-Sun. Contact: Catherine Musemeche, MD, UNM-Division of Pediatric Surgery, 2211 Loma Blvd NE, Albuquerque 87131.

October 3-6—**Building "Virtual" Integrated Delivery Systems: Thriving in an Advanced Healthcare Market.** Pyramid Hotel, Albuquerque. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

October 10-13—**The Managed Care Tool Box.** Pyramid Hotel, Albuquerque. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

October 25-26—**ECG Interpretation for the Primary Care Physician.** Journal Center, Albuquerque. Fri-Sat. Contact: Megan Slane, Course Coordinator, New Mexico Heart Institute, 1001 Coal Ave, SE, Albuquerque 87106. (505) 841-1000; (800) 715-6644. FAX (505) 224-7085.

February 28-March 1—**25th Annual New Mexico Thoracic Society Lung Disease Symposium.** Taos. Fri-Sat. Contact: Billie Dytzel, 216 Truman NE, Albuquerque 87108. (505) 265-0732; (800) 221-LUNG. FAX (505) 260-1739.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

(Continued on Page 89)

In Memoriam

California Medical Association

Acton, William E., Anaheim. Died May 7, 1996, aged 74. Graduate of University of Southern California, Los Angeles, 1957. Licensed in California in 1959. Dr Acton was a member of the Orange County Medical Association.

Ascher, David S., Santa Ana. Died May 17, 1996, aged 83. Graduate of Tufts University School of Medicine, Boston, Massachusetts, 1938. Licensed in California in 1953. Dr Ascher was a member of the Orange County Medical Association.

Bronson, Jeffrey Lawrence, San Diego. Died Jun 14, 1996, aged 51. Graduate of University of Cincinnati College of Medicine, Cincinnati, Ohio. Dr Bronson was a member of the San Diego County Medical Society.

Busby, Dennis R., Santa Barbara. Died Jun 22, 1996, aged 58. Graduate of University of California, San Francisco, School of Medicine, 1963. Licensed in California in 1964. Dr Busby was a member of the Santa Barbara County Medical Society.

Goetsch, Carl, Santa Rosa. Died Jul 3, 1996, aged 85. Graduate of University of Rochester School of Medicine, Rochester, New York, 1937. Licensed in California in 1946. Dr Goetsch was a member of the Alameda-Contra Costa Medical Association and a past president of the California Medical Association.

Green, Robert S., Oakland. Died Feb 14, 1996, aged 89. Licensed in California in 1934. Graduate of University of Arkansas School of Medicine, Little Rock, 1933. Licensed in California in 1934. Dr Green was a member of the Alameda-Contra Costa Medical Association.

Hodge, James J., Orange. Died Jun 24, 1996, aged 56. Graduate of Ohio State University College of Medicine, Columbus, 1964. Licensed in California in 1965. Dr Hodge was a member of the Orange County Medical Association.

Johnson, Francis T., Monrovia. Died Mar 5, 1996, aged 90. Graduate of University of Colorado School of Medicine, Denver, 1930. Licensed in California in 1931. Dr Johnson was a member of the Los Angeles County Medical Association.

Johnson, Kenneth M., Sacramento. Died Jun 26, 1996, aged 92. Graduate of University of California, San Francisco, School of Medicine, 1934. Licensed in California in 1940. Dr Johnson was a member of the Sacramento-El Dorado Medical Society.

Kelly, William L., Las Vegas, Nevada. Died Jan 21, 1996, aged 64. Graduate of New York Medical College, New York, 1958. Licensed in California in 1979. Dr Kelly was a member of the Orange County Medical Association.

Kinsman, Robert G., Fullerton. Died Jun 4, 1996, aged 71. Graduate of George Washington University School of Medicine, Washington, DC, 1953. Licensed in California in 1954. Dr Kinsman was a member of the Orange County Medical Association.

Ledwich, Thomas W., Napa. Died Jun 2, 1996, aged 73. Graduate of University of California, San Francisco, School of Medicine, 1946. Licensed in California in 1947. Dr Ledwich was a member of the Napa County Medical Society.

Lizardi, Hector, San Jose. Died Nov 2, 1995, aged 71. Graduate of University of Tennessee Center for Health Science, Memphis, 1958. Licensed in California in 1959. Dr Lizardi was a member of the Santa Clara County Medical Association.

Millar, Glenn C., San Luis Obispo. Died Jul 15, 1996, aged 68. Graduate of George Washington University School of Medicine, Washington, DC, 1953. Licensed in California in 1956. Dr Millar was a member of the San Luis Obispo Medical Society.

Rajala, A. I., Santa Barbara. Died Jun 24, 1996, aged 75. Graduate of University of Minnesota Medical School, Minneapolis, 1951. Licensed in California in 1968. Dr Rajala was a member of the Santa Barbara County Medical Society.

Roach, Robert W., San Diego. Died Jun 1996, aged 81. Graduate of Indiana University School of Medicine, Indianapolis, 1952. Licensed in California in 1953. Dr Roach was a member of the San Diego County Medical Society.

Seleski, George A., Sacramento. Died May 24, 1996, aged 74. Graduate of Albany Medical College, Albany, New York, 1945. Licensed in California in 1948. Dr Seleski was a member of the Sacramento-El Dorado Medical Society.

Stafford, Richard L., Huntington Beach. Died May 13, 1996, aged 69. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1962. Licensed in California in 1963. Dr Stafford was a member of the Orange County Medical Association.

Vigo, Anthony, Napa. Died Jun 14, 1996, aged 81. Graduate of St Louis University School of Medicine, St Louis, Missouri, 1946. Licensed in California in 1953. Dr Vigo was a member of the Napa County Medical Society.

Ward, Walter, San Francisco. Died Mar 26, 1996, aged 84. Graduate of University of Southern California, 1944. Licensed in California in 1944. Dr Ward was a member of the Alameda-Contra Costa Medical Association.

Williams, S. Randall, Manteca. Died Jul 22, 1996, aged 49. Graduate of University of Texas, Southwestern Medical School, Dallas, 1972. Licensed in California in 1975. Dr Williams was a member of the San Joaquin County Medical Society.

Zetterlund, Russell P., San Diego. Died May 31, 1996, aged 64. Graduate of Boston University School of Medicine, Boston, Massachusetts, 1957. Licensed in California in 1961. Dr Zetterlund was a member of the San Diego County Medical Society.

New Mexico Medical Society

Baker, Maria L., Albuquerque. Died Jul 9, 1996, aged 41. Graduate of University of New Mexico, Albuquerque, 1984. Licensed in New Mexico in 1987. Dr Baker was a member of the Greater Albuquerque Medical Association.

Miller, Eric R., Albuquerque. Died May 15, 1996, aged 47. Graduate of University of Southern California, Los Angeles, 1977. Licensed in New Mexico in 1978. Dr Miller was a member of the Greater Albuquerque Medical Association.

Spitz, Theodore, Albuquerque. Died Jul 3, 1996, aged 81. Graduate of School of Medicine of Royal Colleges, Scotland. Licensed in New Mexico in 1949. Dr Miller was a member of the Greater Albuquerque Medical Association.

Articles

A Cluster of *Escherichia coli* O157:H7 Infections With the Hemolytic-Uremic Syndrome and Death in California

A Mandate for Improved Surveillance

ABIGAIL M. SHEFER, MD, *and* DENISE KOO, MD, *Atlanta, Georgia;* S. BENSON WERNER, MD, *Berkeley, California;* ERIC D. MINTZ, MD; ROY BARON, MD; JOY G. WELLS, PhD; *and* TIMOTHY J. BARRETT, PhD, *Atlanta, Georgia;* MICHELE GINSBERG, MD, *San Diego, California;* RAY BRYANT, PhD, *and* SHARON ABBOTT, PhD, *Berkeley, California; and* PATRICIA M. GRIFFIN, MD, *Atlanta, Georgia*

In mid-January 1993, an outbreak of *Escherichia coli* O157:H7 infections associated with eating hamburger patties at a fast-food restaurant chain (chain A) was reported in Washington State. From mid-December to mid-January, 9 cases of *E coli* O157:H7–associated bloody diarrhea and the hemolytic-uremic syndrome had been reported in San Diego County, California. A total of 34 persons had bloody diarrhea, the hemolytic-uremic syndrome, or *E coli* O157:H7 organisms isolated from stool during the period November 15, 1992, through January 31, 1993. Organisms of *E coli* O157:H7 identified from 6 persons were indistinguishable from those of the Washington outbreak strain. Illness was associated with eating at chain A restaurants in San Diego (odds ratio, 13; 95% confidence interval, 1.7, 99) and with eating regular-sized hamburgers (odds ratio, undefined; lower-limit 95% confidence interval, 1.3). Improved surveillance by mandating laboratory- and physician-based reporting of cases of *E coli* O157:H7 infection and the hemolytic-uremic syndrome might have alerted health officials to this outbreak sooner, which could have resulted in earlier investigation and the institution of measures to prevent more cases.

(Shefer AM, Koo D, Werner SB, et al: A cluster of *Escherichia coli* O157:H7 infections with the hemolytic-uremic syndrome and death in California—A mandate for improved surveillance. West J Med 1996; 165:15-19)

Escherichia coli O157:H7 was first identified as a pathogen in 1982 during an investigation of two outbreaks of bloody diarrhea in Michigan and Oregon.[1] It is now recognized as an important cause of the hemolytic-uremic syndrome and acute renal failure.[2] In prospective studies, *E coli* O157:H7 was identified from more than 85% of children with the hemolytic-uremic syndrome whose stool specimens were collected soon after the onset of diarrhea.[3,4] A population-based study from Washington State showed an increasing incidence of the hemolytic-uremic syndrome from the 1970s to 1980s, suggesting that the incidence of disease due to *E coli* O157:H7 may be increasing.[5]

From mid-November 1992 through mid-January 1993, the San Diego County Department of Health Services learned of nine persons with bloody diarrhea or the hemolytic-uremic syndrome; *E coli* O157:H7 was identified in stool specimens of six. Initial interviews found that four of them had eaten at one restaurant chain (chain A), but an equal number reported eating at another restaurant chain (chain B). It was initially unclear whether this was an outbreak of *E coli* O157:H7–associated illness because most cases lacked a common food source, and because there was no surveillance system for *E coli* O157:H7 or the hemolytic-uremic syndrome, background rates of illness were unknown. An intensive investigation was begun only after an outbreak associated with chain A was recognized in Washington State in mid-January[6-8] and it was determined that meat from the implicated lots may have also been distributed in southern California. The chain A–associated outbreak in Washington State was subsequently found to be linked to specific lots of ground meat produced on November 19, 1992.[8]

From the Division of Field Epidemiology, Epidemiology Program Office (Drs Shefer and Baron), and the Foodborne and Diarrheal Diseases Branch, Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases (Drs Koo, Mintz, Wells, Barrett, and Griffin), Centers for Disease Control and Prevention, Atlanta, Georgia; the Division of Communicable Disease Control, California Department of Health Services, Berkeley, California (Drs Werner, Bryant, and Abbott); and the San Diego Department of Health Services, San Diego, California (Dr Ginsberg).

This article is based on a paper that was presented in part at the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, Louisiana, October 1993 (abstract No. 1278).

Informed consent was obtained from parents or guardians of all participants.

Reprint requests to Abigail M. Shefer, MD, Mailstop E-52, National Immunization Program, Centers for Disease Control and Prevention, 1600 Clifton Rd, Atlanta, GA 30333.

ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control and Prevention
CI = confidence interval
OR = odds ratio

Patients and Methods

Epidemiologic Investigation

We defined a case of *E coli* O157:H7 infection as illness in a resident of San Diego County during the period November 15, 1992, through January 31, 1993, with one or more of the following: bloody diarrhea with three or more loose stools in a 24-hour period, the hemolytic-uremic syndrome with a prodrome of diarrhea, or a stool culture that grew *E coli* O157:H7. We defined a secondary case as illness meeting the case definition in any person who reported that a household member had diarrhea in the week before his or her onset of illness.

Case Finding

Cases were identified through self-reporting, physician referral, or laboratory notification of an *E coli* O157:H7 organism. We reviewed emergency department records at five local hospitals in the northern, central, and southern parts of the county to identify cases during December 1992 and January 1993. We reviewed inpatient and clinic records at the main pediatric hospital in the county that served as a referral center for all cases of the hemolytic-uremic syndrome.

Laboratory Investigation

All case-patients who had not had stool specimens screened for *E coli* O157:H7 were asked to provide stool specimens, which were plated on sorbitol-MacConkey agar.[9] Sorbitol-negative colonies were selected and screened with O157 antisera by tube agglutination. Isolates confirmed as *E coli* through biochemical identification were then screened for immobilization with antisera to the H7 antigen. Organisms were tested for the production of Shiga-like toxins I and II using Vero cell-culture cytotoxicity[10] at the California State Department of Health Services Microbial Diseases Laboratory. Cytotoxic activity was neutralized using monoclonal antibodies against Shiga-like toxin I[11] and polyclonal and monoclonal antibodies against Shiga-like toxin II.[12] Pulsed-field gel electrophoresis was performed at the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia.[13] All case-patients were also asked to provide blood specimens, which were assayed at the CDC for antibody titers to *E coli* O157 lipopolysaccharide by enzyme-linked immunosorbent assay.[14] A positive titer was defined as 1:160 or higher.

First Case-Control Study

To identify risk factors for illness, we conducted a matched case-control study using the first 25 primary case-patients identified. Controls were matched by sex, age (age groups 1 to 4 years, 5 to 9 years, 10 to 19 years, 20 to 29 years, and 30 years and more), and residential location (by adding successive single digits to the case-patient's telephone number). Only persons who denied having diarrhea (3 or more loose stools in a 24-hour period) during the outbreak period were enrolled as controls. Patients and controls were interviewed by telephone with the use of a standard questionnaire.

Second Case-Control Study

To identify food items associated with illness, we used a standard questionnaire to compare foods eaten by case-patients at chain A with those eaten by controls (meal companions) who remained well. Case-patients were matched with their own meal companions; those without meal companions were excluded.

Third Case-Control Study

To identify a possible common source for patients who did not eat at chain A, we conducted a third case-control study including only those patients who were certain they had not recently eaten at chain A. Secondary cases were excluded. Matched controls were selected as in the first case-control study.

Investigation of Restaurants and Microbiologic Testing of Hamburgers

We inspected two franchise and two company-owned chain A restaurants where case-patients had eaten. Food preparation practices were reviewed, particularly the procedures for preparing, cooking, and serving hamburgers. Information about grill types and models used by the 81 chain A restaurants in San Diego County were provided by the Operational Services Department of the parent company.

Specimens from lots of hamburger produced on November 19, 1992, and recalled from southern California and Nevada chain A restaurants were tested at the California Department of Health Services, the United States Department of Agriculture, and the University of Georgia. The following methods were used by the California Department of Health Services. Specimens of hamburger meat were incubated in modified trypticase soy broth and homogenized before passage through sterile hydrophobic grid membrane filters, which were then cultured on sorbitol-MacConkey agar and hemorrhagic-colitis medium plates.[15]

The χ^2 test used to determine matched odds ratios (OR) and exact 95% confidence intervals (CI) was calculated with Epi-Info version 5.0 and the method of Martin and Austin.[16]

Results

Descriptive Epidemiology

In all, 34 persons had illnesses that met the case definition, 10 of whom (29%) were identified through a review of emergency department records, 9 (26%) by reports from physicians, 8 (23%) through self-referral, 6 (18%) from laboratory isolates, and 1 by referral of a friend. Most illnesses began during the period mid-

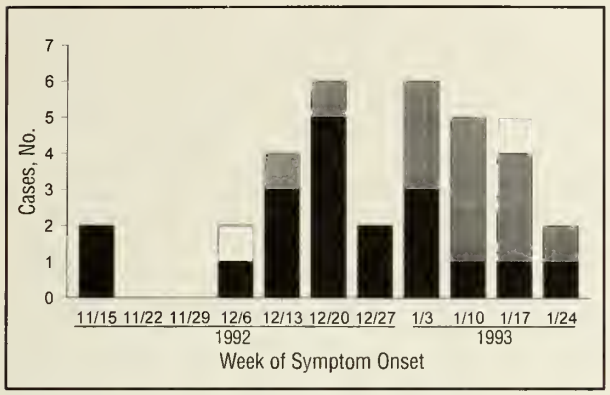

Figure 1.—The graph shows the week of onset of *Escherichia coli* O157:H7–associated illness for 34 cases in San Diego County, California, between November 15, 1992, and January 31, 1993. The black bars indicate case-patients who reported eating at chain A, the shaded bars indicate case-patients who did not report eating at chain A, and the white bars indicate case-patients who did not know if they had eaten at chain A or had secondary transmission.

December through mid-January (Figure 1), although the peak onset of illness was earlier for those patients who reported eating at chain A.

Patients' ages ranged from 1 to 58 years (median, 10 years); 20 (59%) were female. Diarrhea lasted a median of five days (range, 2 to 45 days); 33 patients (97%) described their diarrhea as bloody. Of the 34 persons, 14 (41%) were admitted to a hospital, 7 of whom had the hemolytic-uremic syndrome; one child with the syndrome died with multisystem organ failure. One patient who reported nonbloody diarrhea in a sibling in the week before onset was classified as a secondary case.

Laboratory Investigation

Stool specimens from 31 of the 34 patients were cultured. Of these, 23 were examined for *E coli* O157:H7, and 8 were positive. Of the 15 negative specimens, 13 (87%) were collected either after antibiotic use or more than ten days after the illness began. Of these 15 patients, 12 with cultures negative for *E coli* O157:H7 had cultures negative for *Salmonella, Shigella,* and *Campylobacter* species within three days after the onset of their illnesses. *Clostridium difficile* toxin was reported in the stool of 1 of these 15 patients, but a culture for *C difficile* was negative; this patient had not received antibiotics, and later the hemolytic-uremic syndrome developed. Eleven patients did not have stool specimens examined for *E coli* O157:H7. Stool cultures from eight of these were negative for *Salmonella, Shigella,* and *Campylobacter* species, and the other three had no stool testing. All eight *E coli* O157:H7 isolates produced Shiga-like toxins I and II. Pulsed-field gel electrophoresis revealed an identical electrophoretic pattern in six isolates, the same as that of the Washington outbreak strain. The two other identified organisms had patterns that differed from those of the outbreak strain and each other. Four of the six case-patients with the outbreak strain reported eating at chain A, and another was the secondary case-patient who had not eaten at chain A but whose sibling had eaten there and in whom nonbloody diarrhea developed in the week before the case-patient's illness began. The parents of the sixth case-patient said that their child had not eaten at chain A. One of the patients whose strain differed from the outbreak strain had not eaten at chain A, and the other did not remember.

Serum specimens from 9 of the 29 case-patients tested (31%) had positive antibody titers to *E coli* O157 lipopolysaccharide. Four were from persons with positive stool cultures, and two others were from children with the hemolytic-uremic syndrome. Five patients with the outbreak strain of *E coli* O157:H7 each submitted one serum specimen. Three of these, collected 30, 37, and 50 days after the onset of illness, were positive; two that were collected 4 and 23 days after the onset of the illness were negative. Of the two patients with positive stool cultures for the non–outbreak strains of *E coli* O157, one had a positive antibody titer from a specimen collected 13 days after the illness began, and one had a negative titer from a specimen collected 62 days after the illness began.

First Case-Control Study

Of the 25 primary case-patients, 15 (60%) reported eating at chain A in the ten days before the illness started, compared with 1 (4%) of 25 controls (OR, 13; CI, 1.7, 99; $P = .003$). After the two cases who did not have the outbreak strain of *E coli* O157:H7 and their matched controls were excluded, cases were still significantly more likely to have eaten at restaurant chain A than were controls (OR, 6.0; CI, 1.3, 38.8; $P = .02$). The second most frequently visited fast-food restaurant (chain B) was not significantly associated with illness. Overall, 19 (58%) of the 33 primary cases had eaten at chain A.

Second Case-Control Study

The food selected by the 12 case-patients who ate at chain A was compared with that of 19 well meal companions. Of the 12 case-patients, 10 (83%) ate regular-sized hamburgers compared with 8 (42%) of 19 meal companions (OR undefined; lower limit of 95% CI, 1.3; $P = .008$). No other food item was associated with illness.

Third Case-Control Study

Overall, 17 (89%) of the 19 case-patients who ate at chain A ate a regular-sized hamburger. These were compared with the 15 who did not eat at chain A. The median age was 7 years for the former group and 15 years for the latter ($P = .55$). As seen in Figure 1, the peak of the onset of illnesses was the week of December 20 for the former and the week of January 10 for the latter. These findings suggested that the source or mode of transmission may have differed. We therefore looked for another common source by doing a third matched case-control study that included only patients who did not report eating at chain A. Two patients were excluded: one who was a secondary case, and one who did not remember if he had eaten at chain A. Matched case-control analysis of reported exposures did not show any significant associations (Table 1).

TABLE 1.—*Third Case-Control Study: Exposures Among Case-Patients Who Did Not Eat at Chain A and Their Matched Controls*

Exposure	Cases n = 13, No. (%)	Controls n = 13, No. (%)	Matched Odds Ratio	95% CI
Any restaurant	12 (92)	8 (62)	5.0	0.7-34.0
Hamburger	9 (69)	8 (62)	2.0	0.4-11.0
Restaurant chain B	4 (31)	5 (38)	0.7	0.2-3.3
Meat purchased in store X	8 (62)	9 (69)	0.7	0.1-3.9
Day care	2 (15)	3 (23)	0.5	0.1-5.3
Chicken	9 (69)	11 (85)	0.3	0.1-2.9
Other beef	4 (31)	9 (69)	0.0	0.0-1.2
Turkey	5 (38)	4 (31)	0.0	0.0-0.2

CI = confidence interval

A higher proportion of cases than controls reported having eaten at any restaurant and having eaten hamburger in the ten days before the illness began, but the 95% confidence intervals included one.

Investigation of Restaurants and Microbiologic Testing of Hamburgers

The parent company distributed boxes of frozen patties of raw ground beef from its central distribution center to the 81 chain A restaurants in San Diego County. Of these 81 restaurants, 16 were named by patients. Of these 16 restaurants, 4 (25%) were franchises, and the others were company owned; similarly, 25% of chain A restaurants in the county were franchises. The grill type used in 10 (62%) restaurants named by patients was the same as that used in 53 (65%) chain A restaurants in the county.

Cooking procedures were similar at the two franchise and two company-owned restaurants visited. At both restaurants, regular-sized frozen hamburger patties, which were not prethawed, were cooked during the outbreak for one minute per side.

Investigations in Washington State linked illness to regular-sized hamburger patties produced on November 19, 1992.[6-8] *Escherichia coli* O157:H7 cultured from regular-sized hamburger patties recalled from southern California and Nevada had an electrophoretic pattern that was identical to that of organisms from six patients in San Diego and to those of the Washington outbreak strain. The suspect regular-sized hamburgers had been distributed to chain A restaurants in southern California from December 7 through December 21, 1992 (Jessica Tuttle, MD, Foodborne and Diarrheal Diseases Branch, CDC, Atlanta, Georgia, oral communication, May 1993). A total of 697 boxes containing 278,800 suspect regular-sized patties were distributed in southern California and Nevada; only 42 of these boxes were returned after the company's recall order, which was issued on January 18, 1993; presumably the patties in the other boxes had been eaten (Jessica Tuttle, MD, CDC, oral communication, May 1993).

Discussion

The large proportion of patients in San Diego County who were admitted to a hospital or in whom the hemolytic-uremic syndrome developed suggests that many cases of milder illness were not detected.[2] The lack of routine surveillance for *E coli* O157:H7 in California probably resulted in underrecognition of the magnitude of the outbreak there. Restaurants in southern California used about the same number of the questionable regular-sized patties as those in Washington (Jessica Tuttle, MD, CDC, oral communication, May 1993), but fewer cases were identified. The implicated meat, however, was distributed to about 400 chain A restaurants in southern California, compared with only 64 in Washington State,[8] and the California restaurants were spread over a larger area. Active case finding took place only in San Diego County, where only 20% of the southern California chain A restaurants that received the implicated meat are located. Although California newspapers reported the outbreak, health departments in California did not issue statements recommending that persons with bloody diarrhea visit their physicians so that stool specimens could be appropriately cultured, as was done in Washington. Moreover, few laboratories in California routinely culture stools for this pathogen, and the reporting of *E coli* O157:H7 infection was not required. For example, only two of nine major hospital laboratories surveyed in January 1993 in San Diego County routinely cultured even bloody stools for this organism. In contrast, bloody stools are more frequently cultured for this pathogen in Washington State (Beth Bell, MD, Washington State Department of Health, Seattle, oral communication, May 1993), where mandatory reporting of *E coli* O157:H7 infection was instituted in 1987.[17]

Because the peak of cases in San Diego occurred earlier than the peak in Washington State,[7] identification and recognition of the source of the chain A–associated illnesses in San Diego might have led to measures that could have interrupted the outbreak sooner. There are several possible reasons why the outbreak was not detected sooner in San Diego: *E coli* O157:H7 was not reportable in California, the rate of background infection was not known, and hospitals were not routinely culturing for the organism. Furthermore, interviews of the nine case-patients who were initially reported to the county health department in December did not reveal a restaurant source that was common to most of the cases: four persons had eaten at one restaurant chain, and four had eaten at a different restaurant chain.

We were unable to identify other food sources of infection for persons with illness who did not eat at restaurant chain A. At least some of these cases most likely represent sporadic background cases that occur year-round but could not be documented as such because of the lack of a surveillance system. Although a higher proportion of case-patients than control persons ate at restaurants and ate hamburgers, these trends were not statistically significant. This finding may be attributable partly to small sample size, but several sources of infection are likely. Two patients had *E coli* O157:H7 strains that differed from one another and from the outbreak strain; other patients may also have had another source of

infection or had illness due to another pathogen. The observation, however, that one patient who denied eating at chain A had the outbreak strain suggests that other patients with no known connection to chain A could have been part of the outbreak as well. Some cases may have been misclassified; for example, parents who provided food histories for their ill children may not have known that their children had eaten at a chain A restaurant. Or more cases may have been due to secondary spread than the one recognized. In addition, some of the questionable meat, besides being supplied as patties to restaurant chain A, was distributed as ground beef to other restaurants and to grocery stores in southern California (Jessica Tuttle, MD, CDC, oral communication, May 1993).

The outbreak of *E coli* O157:H7 infections in San Diego County was part of the largest *E coli* O157:H7 outbreak yet recorded, involving four states and causing laboratory-confirmed illness in more than 500 people.[7,8] The magnitude of this outbreak emphasizes the potential for a multistate outbreak when a contaminated product is widely distributed. Improved surveillance for *E coli* O157:H7 and the hemolytic-uremic syndrome is needed so that outbreaks can be recognized and control measures quickly implemented. We recommend that laboratories routinely culture diarrheal stool specimens for *E coli* O157:H7 using sorbitol-MacConkey medium; at a minimum, this pathogen should be sought in the stools of all persons with bloody diarrhea. The serologic test for antibodies to O157 lipopolysaccharide is still experimental, and its sensitivity and specificity vary when used in different settings.[14] Of all patients identified as cases, 31% in our study had elevated antibody titers, compared with 53% of patients in the previous study.[14] The serologic test is done only in reference laboratories and will remain a research tool until the pattern of the serologic response to infection with *E coli* O157:H7 is better characterized.

More outbreaks of *E coli* O157:H7 have been linked to undercooked ground beef than to any other vehicle.[2] Several possible approaches may reduce the risk of illness due to this pathogen in meat products. In response to this outbreak, on January 28, 1993, the Food and Drug Administration issued interim recommendations for the cooking of all ground beef products to at least 68°C (155°F), rather than the previously recommended internal temperature of 60°C (140°F).[18] In addition, the Food Safety and Inspection Service of the United States Department of Agriculture now requires that safe food-handling labels be placed on all packages of raw meat products at the point of retail sale.[19]

Surveillance in California for this pathogen will be improved. Regulations have been proposed to make this infection reportable by both laboratories and health care professionals and to make the hemolytic-uremic syndrome reportable by health care professionals. To improve the timely detection of future outbreaks, though, physicians and laboratory personnel must be educated in the appropriate indications for and methods of testing for this organism. In addition, people who work in the food industry must be educated to cook hamburgers according to current recommendations, and consumers must demand that hamburgers served at home or in restaurants be cooked until no trace of pink color remains.

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Articles

Pediatric Hospital Admissions for Measles
Lessons From the 1990 Epidemic

GILBERTO F. CHAVEZ, MD, MPH, *and* ARTHUR A. ELLIS, MA,* *Sacramento, California*

To examine the descriptive epidemiology of serious measles complications and associated hospital costs during a major epidemic, we used California population-based hospital discharge data to identify hospital admissions for measles during 1986 through 1990 (ICD-9 code 055, n = 4,201). We examined 5-year trends and, for 1990 pediatric epidemic cases (n = 2,234), sociodemographic and hospital admission financial data. Hospital admission rates for measles rose significantly between 1986 and 1990. During the 1990 epidemic, preschool children aged 1 to 5 years, Medi-Cal (California's Medicaid) beneficiaries, Hispanics, and those living in urban counties accounted for most hospital admissions. Young infants and residents of southern California and the San Joaquin Valley had the highest risks. Medi-Cal beneficiaries and Asian children were at an increased risk for death during the hospital stay. The average hospital admission cost was $8,201, and the average length of hospital stay was 4.6 days. Hospital costs amounted to $18 million, two thirds of which was paid for by Medi-Cal. Measles is a serious disease that can result in severe complications requiring lengthy and costly hospital stays. We must remain alert to its continuing threat, complications, and resulting financial burdens.

(Chavez GF, Ellis AA: Pediatric hospital admissions for measles—Lessons from the 1990 epidemic. West J Med 1996; 165:20-25)

Despite a dramatic 98% decrease in the number of measles cases since the measles vaccine was introduced in 1963, measles continues to occur in epidemic and nonepidemic forms in the United States.[1] The United States experienced a large measles epidemic during 1989 and 1990. In 1990, the peak of the epidemic, 27,786 cases of measles were reported (11.2 cases per 100,000 population). The number of reported measles cases declined to 9,643 in 1991 (3.9 per 100,000)[2] and 2,200 in 1992 (0.9 cases per 100,000), suggesting that the most recent resurgence of the disease has ended.[3]

During the 1989-1990 epidemic nationwide, children younger than 5 years had the highest age-specific incidence rates.[4] The outbreaks were confined primarily to large inner-city areas. Unvaccinated, economically disadvantaged minority group children were most at risk.[4] The measles incidence was highest for Native Americans, Hispanics, and blacks and lowest for whites.[1,2,4-8] The epidemic was largely attributed to the failure to vaccinate children at appropriate ages.[9-14,†]

In 1990 California had about 50% of all measles cases in the United States.[10] Statewide, the epidemic occurred predominantly in children younger than 5 years, in low-income minority communities, and in southern California and the San Joaquin Valley.[15] Preschoolers, particularly infants—363.1 per 100,000 compared with an average incidence rate of 26.2 for all 1989-1990 cases—was the predominant age group affected, with most cases occurring among unvaccinated children.[15] Los Angeles, Orange, Riverside, and San Bernardino counties had the largest number of reported cases.[2] The highest rates of measles were observed in Kern, San Bernardino, Merced, Riverside, Fresno, and Tulare counties (Karen Swanson, Immunizations Branch, California Department of Health Services, written communication, December 1995).

Measles complications are an accurate measure of the overall health effects of widespread outbreaks. Serious complications require admission to a hospital. During the nationwide outbreak of 1989-1990, more than 19% of the reported cases of measles required admission to a hospital.[4,15] Despite their importance, little is known about the epidemiology of complicated measles cases.

In this report, we examine the descriptive epidemiology of hospitalized measles cases in California and measure the effects of severe measles among children and the financial burden of hospitalized measles cases on the health care system.

*Authors are listed alphabetically because of equal coauthorship.

†See also the editorial by N. J. Smith, MD, MPH; L. G. Dales, MD, MPH; and S. H. Waterman, MD, MPH, "California's 1988-1991 Measles Epidemic—The Last One?" on pages 80-81 of this issue.

From the Maternal and Child Health Branch, California Department of Health Services (CDHS), Sacramento (Dr Chavez and Mr Ellis), and the Pregnancy and Infant Health Branch, Division of Reproductive Health, National Center for Health Promotion and Chronic Disease Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia (Dr Chavez). Mr Ellis is now with the Emergency Preparedness and Injury Control Branch, CDHS.

Reprint requests to Gilberto F. Chavez, MD, MPH, 714 P St, Rm 476, Sacramento, CA 95814.

ABBREVIATIONS USED IN TEXT

HMO = health maintenance organization
RR = relative risk

Methods and Data

Data Source

We used the population-based California Patient Discharge Data Base, obtained from the California Office of Statewide Health Planning and Development. This data set comprised about 3.5 million hospital discharges per year from all general acute care hospitals (about 590 per year) licensed to serve civilian patients. We identified measles-induced hospital admissions using the *International Classification of Diseases, 9th revision, Clinical Modification*,[16] code 055, for the period 1986 to 1990. To calculate population-based hospital admission rates, we used California Department of Finance population estimates for the denominator. In addition, to calculate the hospital admission rates for measles cases, we used summary measles incidence data provided by the Immunizations Branch, Division of Communicable Disease Control, California Department of Health Services. These data included the number of measles cases by age and county of residence, plus the percentage of patients with measles admitted to a hospital.

A total of 4,201 hospital admissions due to measles were identified during the study five-year period. We excluded patients who transferred from other short-term acute care hospitals to tertiary care centers to avoid duplicating cases. These exclusions ranged from 0 for 1986 to 182 for 1990. Therefore, our figures represent incident hospitalized cases only. To assess the epidemiologic characteristics of pediatric measles cases admitted to a hospital during the 1990 epidemic, we further limited our analysis to all 2,052 hospital admissions occasioned by measles among patients younger than 20 years for this year.

Data Elements

The hospital discharge database variables used in this study were race or ethnicity (white, black, Hispanic, and Asian or other); age in years (infants younger than 1 year, preschool children aged 1 to 4 years, school-aged children 5 to 19 years); expected principal source of payment; principal diagnosis code; as many as five secondary diagnoses codes; total hospital charges, including charges for all services rendered in the hospital, except physician fees; length of hospital stay in days; and disposition at discharge (such as normal, transferred, or died). High data quality and reliability are assured by error tolerance levels for each data element (0.1% for most items) and by periodic reabstracting studies.

Analysis

We calculated trends for the five-year period 1986 to 1990. Hospital admission rates per 100,000 California population were examined by age group and race or ethnicity. For all age groups, we included number of hospitalized cases of measles and total number of reported measles cases. This allowed the computation of case-specific hospital admission rates. We calculated only crude rates because data necessary to calculate adjusted rates were not available. In addition, we computed measles case-specific hospitalization rates according to age, county, and region of residence. To measure the risk for hospitalization, we calculated relative risks (RR) using the lowest risk group as a referent. Statistical significance was determined using 95% confidence intervals. Asians were combined with "other" to be comparable with California population data and made up 84.2% of the category. The most common comorbid conditions were determined by aggregating the second through the fifth diagnoses after the admitting diagnosis. For deaths occurring during the hospital stay, we give death-to-hospitalized case ratios per 1,000 hospital admissions by age group. We examined measles-related mortality by type of health insurance to assess the association of socioeconomic status with hospital mortality.

Using available data on hospital admission charges and length of stay, we estimated the total costs of measles hospitalizations, average charge per hospital admission, average number of days in hospital, and total number of days by type of health insurance coverage among the 1990 cases. Computations of the averages were based on all hospitalized measles cases with hospital cost information (95.9%). Excluded were 92 cases with unknown or unreported cost information, principally (94.6%) health maintenance organization (HMO) patients. Kaiser Permanente, the largest HMO in California, was exempt from reporting hospital costs. Cost information was limited to inpatient charges and excludes physician fees.

TABLE 1.—*Hospital Admission Rate for Measles in California, 1986 to 1990**

Year	Measles Hospital Admissions, No.	Reported Measles Cases, No.	Case-Specific Hospital Admissions Rate/10^2 Cases (95% CI)	Hospital Admission Rate/10^6 Residents (95% CI)
1986	38	456	8.3 (5.8, 10.9)	0.1 (0.1, 0.2)
1987	40	813	4.9 (3.4, 6.4)	0.1 (0.1, 0.2)
1988	192	818	23.5 (20.6, 26.4)	0.7 (0.6, 0.8)
1989	994	3,061	32.5 (30.8, 34.1)	3.4 (3.2, 3.8)
1990	2,937	12,616	23.2 (22.5, 23.9)	9.8 (9.4, 10.2)

CI = confidence interval

*From the California Office of Statewide Planning and Development Hospital Discharge Data Program; Department of Health Services, Division of Communicable Disease Control, and Department of Finance, Demographic Research Unit.

Results

Recent Trends

As shown in Table 1, the number of hospital admissions in California due to measles rose dramatically from 38 in 1986 to 2,937 in 1990. The case-specific hospital admission rate increased unevenly, from 8.3 per 100 measles cases in 1986 to 23.2 in 1990, with a peak of 32.5 in 1989. The population-based hospital admission rate per 100,000 increased from 0.1 in 1986 to 9.8 in 1990.

TABLE 2.—*Measles Hospitalizations by Age and Race or Ethnicity Among Children and Adolescents in California, 1990**

Characteristic	Hospital Admissions, No.	Rate/10⁵ Population (95% CI)
All cases 0 to19 years old . . .	2,052	23.3 (22.3, 24.3)
Age group, yr		
<1.	669	122.2 (112.9, 131.4)
1-4	1,050	54.0 (50.7, 57.2)
5-19	333	5.3 (4.7, 5.8)
Race or ethnicity		
White	470	11.6 (10.6, 12.6)
Black.	286	40.4 (35.8, 45.1)
Hispanic	1,125	36.2 (34.1, 38.3)
Asian and other†.	171	18.3 (15.6, 21.1)

CI = confidence interval

*From the California Office of Statewide Planning and Development Hospital Discharge Data Program and the California Department of Finance, Demographic Research Unit.

†Asians represent 84.2% (144) of this category.

Hospital Admissions for Patients Younger Than 20 Years

Of all hospital admissions for measles in 1990, 70% occurred among those 19 years of age and younger. Nearly a third (32.6%) were infants younger than 1 year, a majority (51.2%) were preschool children aged 1 to 4 years, and the rest (16.2%) were school-aged children 5 to 19 years old (Table 2). The population-based hospital admission rate was 23.3 per 100,000 children. An inverse relationship between age and hospital admission rates was observed. The youngest group had the highest rate (122.2 per 100,000), whereas the rate decreased to 54.0 and 5.3 for the 1 to 4 years and 5 to 19 years age groups, respectively.

Hispanic children constituted a majority (54.8%) of the measles cases admitted to a hospital, followed by whites (22.9%), blacks (13.9%), and Asians and other (8.3%). When assessing these data on a population basis, however, the hospital admission rate was highest for blacks, followed by Hispanics and Asians and other (see Table 2). Whites had the lowest rate.

As shown in Table 3, infants and children aged 1 to 4 years had the highest measles case-specific hospital admission rates. Their risk for hospital admission was 150% higher than that for older children and adolescents (RR = 2.54 and 2.46, respectively). Children residing in southern California had the highest case-specific hospitalization rates, followed by those residing in the San Joaquin Valley and the San Francisco Bay Area or Central Coast. Compared with children in the northern California and Sierras regions, those residing elsewhere in the state had significantly elevated risks for hospital admission. Children residing in southern California and the San Joaquin Valley were significantly at the highest risk for admission to a hospital (RR = 2.94 and 2.24, respectively).

TABLE 3.—*Measles Case-Specific Hospital Admission Rates by Age and Geographic Region Among Children and Adolescents in California, 1990**

Characteristic	Case-Specific Hospital Admission. Rate/100 Cases	Relative Risk (95% CI)
Age group, yr		
<1	26.1	2.54 (2.25, 2.86)
1-4.	25.3	2.46 (2.19, 2.76)
5-19.	10.3	1.00†
Region‡		
Southern California	27.1	2.94 (1.91, 4.52)
San Joaquin Valley	20.7	2.24 (1.45, 3.47)
San Francisco Bay Area and Central Coast	14.8	1.61 (0.99, 2.60)
Northern California and Sierras	9.1	1.00†

CI = confidence interval

*From the California Department of Health Services, Division of Communicable Disease Control, Immunization Branch, Mandatory Disease Reports.

†Referent group.

‡*Southern California:* Imperial, Los Angeles, Orange, Riverside, San Bernardino, San Diego, Santa Barbara, and Ventura counties; *San Joaquin Valley:* Fresno, Kern, Kings, Madera, Merced, San Joaquin, Stanislaus, and Tulare counties; *San Francisco Bay Area and Central Coast:* Alameda, Contra Costa, Marin, Monterey, Napa, San Benito, San Francisco, San Luis Obispo, San Mateo, Santa Clara, Santa Cruz, Solano, and Sonoma counties; *Northern California and Sierras:* all other counties.

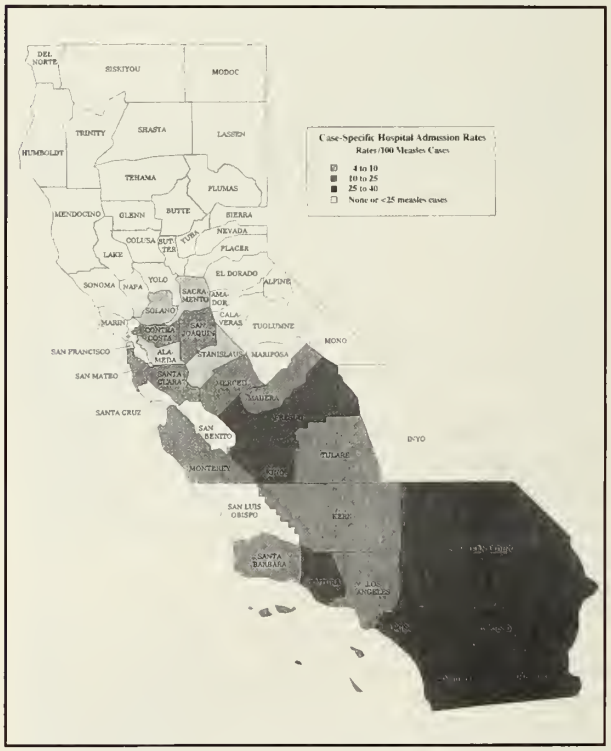

Figure 1.—Measles case-specific hospital admission rates for the 1990 epidemic are shown by California counties.

Figure 1 shows the case-specific hospitalization rates among measles cases throughout the 58 counties in the state. Among counties with at least 25 measles cases, hospital admission rates ranged from a high of 37.4 per 100 in San Bernardino County to a low of 4.9 per 100 in Stanislaus County. A pronounced geographic clustering of high case-specific hospitalization rates was observed in southern California and San Joaquin Valley counties.

Hospitalized Cases by Type of Complication

Few comorbid conditions were substantial contributors to hospital admissions for measles in 1990 (Table 4).

The most common complications resulting from measles were either a result of fluid loss, secondary infection, or acute organ involvement. The main complication was a disorder of fluid, electrolyte, and acid-base balance found in nearly a third of the cases. Further analysis of the specific diagnoses among these cases showed that nearly all of them were due to volume depletion. Otitis media was the second largest complication, present in nearly a fifth of the patients.

Measles-Associated Deaths

A total of 22 children died in hospital, for a death-to-hospitalized case ratio of 1%. The primary cause of death among these children was measles pneumonia. Of the deaths, 15 (68%) were in the 1 to 4 years age group, with the ratio being 1.3 (compared with 0.7 and 0.6 among infants younger than 1 and children aged 5 to 19 years, respectively). Children who were Medi-Cal beneficiaries had an increased mortality risk and accounted for 86% of the deaths (19 of the 22 deaths) when they were 62% of cases. Asian children had the highest mortality risk, accounting for 41% of all measles deaths and only 8% of the hospitalized cases. All other racial or ethnic groups were underrepresented in measles-related mortality. Residents of Fresno County were overrepresented among measles-related deaths, with 32% of all deaths and 6% of all hospitalized cases.

TABLE 4.—*Measles Complications Among Hospitalized Children Aged 0 to 19 in California, 1990**

Complication	*Hospital Admissions, No.*	*(%)*
Disorder of fluid, electrolyte, and acid balance	652	(31.8)
Otitis media	382	(18.6)
Acute laryngitis and tracheitis	176	(8.6)
Noninfectious enteritis and colitis	170	(8.3)
Pneumonia	133	(6.5)
Multiple others	539	(26.3)
Total	2,052	(100.0)

*From the California Office of Statewide Planning and Development Hospital Discharge Data Program.

Hospital Costs and Length of Hospital Stay

For all patients younger than 20 years admitted to a hospital for measles during 1990, the average number of days in hospital was 4.6 and the average cost per hospital stay was $8,201 (Table 5). The preschool-aged group had the highest average cost ($9,034), the highest total costs for hospital admission ($10.1 million, 57.3% of the total), and the highest number of days in the hospital (5,280, 54.2% of total). The average number of days in hospital was 4.7 among preschoolers. As also shown in Table 5, the infant group younger than 1 year also had higher hospital costs and longer hospital stays than the oldest group. The total cost of the hospital stay for the 9,742 hospital days among all pediatric cases amounted to $17.6 million. To estimate the hospital costs for the 92 cases with unreported or unknown cost information, we used the average hospital cost for HMO cases because the preponderance were such cases. Combining the estimated $413,372 with our original amount resulted in a rounded total of $18 million (in 1990 dollars).

TABLE 5.—*Hospital Costs and Length of Stay by Age Group and Health Insurance Coverage Among California Children and Adolescents With Measles Admitted to a Hospital, 1990*†*

Age Group, yr, by Insurance Coverage, No.	*Average Cost/ Hospital Admission, $*	*Total Costs for Hospital Admissions, $ × 10³*	*Average Days in Hospital, No.*	*Total Days, No.*
<1	8,374	5,987	4.7	3,357
Medi-Cal	9,438	4,700	5.0	2,463
Private insurance	5,652	384	4.0	271
HMO	4,288	274	3.4	220
Self-pay	8,129	553	4.9	332
Other	4,454	76	4.2	71
1-4	9,034	10,073	4.7	5,280
Medi-Cal	10,634	8,018	5.1	3,837
Private insurance	5,140	6,940	3.8	517
HMO	5,062	557	3.7	404
Self-pay	7,006	581	4.4	367
Other	6,745	223	4.7	155
5-19	4,827	1,506	3.5	1,105
Medi-Cal	5,099	607	3.5	421
Private insurance	4,665	345	3.5	259
HMO	3,707	234	3.1	198
Self-pay	5,280	169	3.7	117
Other	6,307	151	4.6	110
All ≤19	8,201	17,566	4.6	9,742

HMO = health maintenance organization

*From the California Office of Statewide Planning and Development Hospital Discharge Data Program.

†Computation based on cases with hospital cost information (95.9%). For the remaining 92 cases (24, <1 year; 32, 1-4 years; and 36, 5-19 years), charges were unknown or not reported. Of the exclusions, 87 (94.6%) were HMO cases.

Medi-Cal, California's Medicaid program, was the predominant health insurance, accounting for 61.5% of measles cases (Medi-Cal's percentage of all hospital discharges statewide was 19%). Two thirds (67.4%) of hospital admissions among infants younger than 1 year were paid for by Medi-Cal, with the percentage decreasing to 34.2% among those 5 to 19 years. In contrast, for HMOs (14.5%) and private insurance (12.4%), the percentage of cases climbed as age increased.

Overall, Medi-Cal had the highest average and total costs for hospital admissions for measles ($13.3 million, 75.8% of the total). In addition, Medi-Cal also had the largest number of hospital days (6,721, 69% of the total). It had the highest average cost per hospital stay and longest average length of hospital stay for infants and preschoolers. Self-pay patients, representing only 8.3% of the measles cases younger than 20 years, had the second highest average cost per hospital stay and average number of hospital days among infants.

Discussion

Our study developed an epidemiologic profile of children admitted to a hospital for the treatment of measles and its complications that is consistent with the epidemi-

ologic profile observed among all children with measles.[4] We found that infants and young children, Medi-Cal beneficiaries, Hispanics, and residents of urban counties accounted for most of the hospitalized measles cases. In addition, we found that the risk for hospital admission among measles cases was highest among children younger than 5 years, which decreased with increasing age, and those residing in southern California and the San Joaquin Valley. Last, our study underscored that measles is a serious disease that can result in severe complications leading to lengthy and costly hospital stays.

Some limitations of our study need to be considered when interpreting these results. The information collected during the study period on the incidence of measles lacks enough detail to allow for the assessment of risk for measles hospital admissions according to race or ethnicity and type of health care coverage. As a result, we were unable to adjust our hospitalization rates for possible confounders to define key independent risk factors. Nonetheless, the descriptive nature of our study allowed us to obtain valuable information on measles severity and the epidemiologic profile of those at risk for measles complications. In addition, our financial data were limited to hospital charges alone. We cannot account for other costs associated with measles and its complications, such as physician fees and outpatient care. Last, we lacked enough clinical detail on the database to measure the immunization status of children admitted to hospital to identify the proportion of hospital admissions due to vaccine failure or the lack of vaccination.

Before 1988, hospital admissions among children with measles were relatively rare in California. The measles epidemic that peaked in 1990 had its onset in 1988 in Los Angeles County[15] and spread quickly to the rest of the state. With the resurgence of measles in 1988, we observed what might be an increase in measles severity. Children with measles were almost five times more likely to be admitted to a hospital during the epidemic years than during the preceding year. In addition, case-fatality rates among hospitalized children were high during the epidemic period, particularly among Asians and Medi-Cal beneficiaries. This finding is consistent with published reports of high fatality rates among the poor and Samoan and Hmong children with measles.[15] Possible explanations for this increase in measles severity are not clear. We speculate that the high proportion of measles cases among infants and young children, in whom measles is usually more severe, could have greatly contributed to increased severity during the epidemic. In addition, changes in the demographic composition of cases, the underreporting of mild cases during epidemic years, and problems with access to medical care among low-income communities could have played a substantial role. The contribution of a delayed onset of primary care to the risk of hospital admission is not clear. Nonetheless, a lack of early, ongoing, adequate primary care could have played a role, at least in some minority and low-income persons who traditionally either underuse services or have more limited access to primary care. Last, the possibility exists that children may be more freely admitted to a hospital during an epidemic without regard to measles severity. Stratifying our data by days of hospital stay showed, however, that 82% of patients with measles stayed in the hospital for three days or more. Furthermore, the long average length of hospital stay among measles cases supports the notion of high severity during the epidemic.

Nationwide studies show that measles outbreaks have been largely confined to large inner-city areas.[2,4,6,8,9,11] In our study, we found that the case-specific hospital admission rates for measles were substantially higher in counties located primarily in southern California and the San Joaquin Valley. Furthermore, hospital admission rates were high in both large and small communities. We were unable to determine if rates in some counties with large rural areas were primarily among residents of the larger cities within the county. A report in the literature has documented that the recent influx of immigrants into California's rural communities, such as the Hmong and Hispanics, who do not traditionally immunize their children and have limited access to health insurance, has contributed to the increased risk for measles in some areas of the state.[15]

We also found that hospital admissions for measles primarily affected economically disadvantaged and very young children. The greatest majority of pediatric measles cases admitted to a hospital and measles-associated deaths occurred in Medi-Cal beneficiaries or patients who had no health insurance coverage. This observation, coupled with the higher incidence of measles and measles-related hospital stays among racial or ethnic minorities and very young children and infants during the epidemic, suggests the necessity to become sensitive to the health care needs and cultural realities of economically disadvantaged and minority communities. We suggest that the development of effective, culturally sensitive prevention measures targeting these communities may avert the social and financial burdens of measles and its complications. Because most of the costs of hospital admissions for measles were paid for by the public sector, implementing programs that target these communities can possibly save scarce public health care funding.

Although we were unable to do an in-depth cost-benefit analysis because of lack of information, our study showed that the measles epidemic of 1990 resulted in substantial hospital costs and lengthy hospital stays among children with measles. Moreover, using 1990 estimates for vaccinating a child,[10] we estimated that more than 290,000 children could have been vaccinated with the $18 million spent on hospital costs for the treatment of measles and its complications alone.

To our knowledge, this is the first statewide epidemiologic study of hospital admissions due to measles during a large epidemic. We found that young, minority, and economically disadvantaged children residing in southern California and the San Joaquin Valley were most likely to have serious cases of measles requiring admission to a hospital. We also documented that California's public medical sector had to pay for most hospital costs associ-

ated with the epidemic. Moreover, we showed that children admitted to a hospital for the treatment of measles complications had a variety of serious problems requiring lengthy and costly hospital stays and resulting in increased mortality. Measles is clearly not a trivial illness and has substantial morbidity and mortality associated with its occurrence in large outbreaks. We must remain vigilant to the potential for serious complications when measles develops and the need to effectively use appropriate primary prevention measures.

Acknowledgment

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Articles

Patient Preferences for Management of Localized Prostate Cancer

DENNIS J. MAZUR, MD, PhD, *and* DAVID H. HICKAM, MD, MPH, *Portland, Oregon*

We designed this study to determine whether patients with early localized prostate cancer prefer surgical intervention over watchful waiting, which aspects of the 2 management strategies influence patient preferences, and whether there are patient characteristics that predict their preferences for 1 strategy over the other. Structured interviews were used with 140 male patients seen consecutively at a university-based Department of Veterans Affairs Medical Center outpatient clinic. The mean age of the patients was 66.3 years. Of the 140 patients, 53% preferred surgical treatment, 42% preferred observation, 4% preferred that their physician make the decision, and 1% preferred radiotherapy. Of 74 patients selecting surgical intervention, 92% (68) reported that the possibility of complete tumor removal was the strongest factor influencing their decision. Of those selecting observation, 80% (47/59) reported being most influenced by the complications of an operation. Older patients were significantly ($P < .002$) more likely to prefer expectant management. We conclude that tumor excision is an important factor influencing patient preferences for treatment, irrespective of survival benefits. This factor should be considered when designing approaches to providing information to patients about alternative treatments.

(Mazur DJ, Hickam DH: Patient preferences for management of localized prostate cancer. West J Med 1996; 165:26-30)

When considering the management of patients with cancer, it must be decided how aggressively to pursue the surgical excision of the primary tumor. In patients with obvious metastatic spread, the benefits of excision may be limited and often do not outweigh the risks of a surgical procedure. In patients with apparent early-stage disease, however, the decision is influenced by many factors, including the rapidity of tumor growth if not excised, the likelihood of tumor recurrence after excision, disfigurement caused by an operation, the risks of complications or death after an operation, and patient attitudes about facing uncertain outcomes.

Previous research about treatment options has focused primarily on choices between alternative treatments that differ in their short-term and long-term survival benefits.[1-6] For example, in the case of lung carcinoma,[7-9] surgical intervention has a higher short-term probability of death and a better long-term (5-year) survival than the alternative treatment, radiation therapy. We previously did a study in which patients were asked to consider their treatment preferences based on graphic data displays (5-year-survival curve comparisons) derived from research on stage IIb prostate cancer. We found that patients were willing to forgo better five-year survival when offered a treatment option with a lower chance of short-term complications (urinary incontinence and impotence).[10]

In early-stage, low-grade, clinically localized prostate cancer, the issues that have most influenced the discussion of treatment options are the rate of tumor growth in the absence of treatment and the morbid complications associated with surgical treatment. Radical surgical excision for this disease has not had a clinically important effect on long-term survival for older men.[11] Efforts to increase early detection and intervention for prostate cancer have not decreased morbidity and mortality rates compared with expectant management (watchful waiting).[12-14] Some researchers have argued that a randomized clinical trial of alternative treatments is needed,[15] whereas others have concluded that differences in management strategies are important only if a patient has a life expectancy of longer than ten years.[16]

Patients' preferences for active intervention probably influence their choice of treatment. In an attempt to learn about patients' preferences relevant to treatment choices, we studied patients' attitudes regarding the choice of surgical intervention or observation (expectant management or watchful waiting) for early localized prostate cancer. We sought to answer three questions:

- Would patients prefer one strategy over the other; specifically, would they prefer surgical intervention or "expectant management" if they had been diagnosed as having the earliest detectable form of prostate cancer?

From the Medical Service and Health Services Research and Development, Department of Veterans Affairs Medical Center, Portland, Oregon.

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Reprint requests to Dennis J. Mazur, MD, PhD, Medical Service (111-P), Dept of Veterans Affairs Medical Center, 3710 SW US Veterans Hospital Rd, Portland, OR 97201.

• What are aspects of the two management strategies that patients report most influence their preferences?

• Do demographic characteristics of patients influence their preference for one management strategy over the other?

Patients and Methods

This study was approved by the Subcommittee on Human Studies of the Department of Veterans Affairs Medical Center, Portland, Oregon. Consecutive patients being seen for continuity of care in the general medicine clinic were asked before their scheduled clinic visit to participate in a structured interview about decision making. One of us (D.J.M.) conducted the interviews. All patients whose medical records indicated cognitive problems were excluded from the study. Patients who presented to the general medicine clinic in moderate or severe pain or who were in moderate or severe emotional distress were also excluded from the study.

The study was designed to compare two treatment management alternatives for localized prostate cancer: surgical treatment and expectant management (no intervention until symptoms were detected either locally, regionally, or metastatically). The descriptions provided to subjects tended to be biased against surgical treatment. For surgical treatment, we used the verbal probability expression "possible" to describe the likelihood that an operation could remove the tumor completely. We did not specify that surgical treatment "cured" the tumor. We listed the complications of an operation using numerical probability terms represented in percentages. For expectant management, we used the verbal probability term "not possible" to describe the likelihood that the tumor could be removed in its entirety from the body. We specified that in expectant management, the tumor most likely would have extended—either locally (that is, within the prostate), regionally (for example, in an organ adjacent to the prostate, such as the bladder), or through metastasis (spread) elsewhere in the body (such as to bone)—by the time symptoms developed.

Questionnaire Format

Patients were first given a written scenario. All descriptions of the procedures were derived from the current literature on surgical treatment and expectant management in major medical centers where the treatments are studied.[11-15] All risks related to surgical intervention for early prostate cancer were derived from the published literature regarding prostate cancer.[11-15] To bias the study against surgical treatment, we selected the rates that were on the high end of the ranges published in the surgical literature. To ensure that the patients read through the entire scenario before formulating their preference for treatment and to solicit any questions the patients may have about the scenario, the scenario was read aloud to each patient.

Patients were asked to imagine that they had been diagnosed as having the earliest detectable stage of prostate cancer. They were told that prostate cancer is usually slow growing and that there are two management strategies available: surgical intervention and expectant management (watchful waiting). Patients were also told to assume that scientific studies completed to date have not demonstrated a survival difference between surgical therapy and watchful waiting for early prostate cancer at one, two, three, four, and five years and beyond. Patients were then given the following descriptions of each management strategy.

Surgery.

• The operation can be done right away, without delay.

• It is possible that all the cancer will be removed.

• Surgery has a set of complications associated with it:

Rate of Possibility, %	*Complication*
1 to 2	Chance of death
8 to 14	Chance of strictures (narrowing) of the bladder and urethra that may require dilatation or opening by a surgical procedure
6 to 10	Chance of total loss of bladder control that requires wearing a pad or plastic appliance strapped to the leg to collect urine; this pad must be changed 3 to 4 ×/day, or the appliance must be cleaned regularly and emptied 3 to 4 ×/day
10 to 25	Chance of partial loss of bladder control requiring changing the pad or appliance less frequently than with total loss of bladder control
30 to 50	Chance of total impotence (loss of erection of the penis)

Expectant management.

• It is not possible that all the cancer will be removed because nothing is done to the tumor right away, and the tumor is allowed to grow.

• Initially there are no complications because no treatment is undertaken.

• Treatment is delayed, and when symptoms of the tumor occur, one of three management strategies can be undertaken: surgical therapy, radiation therapy, or no further treatment. Symptoms could be due to tumor growth locally within the prostate gland or regionally to organs around the prostate (such as the bladder). Symptoms could also result from the tumor that has metastasized (spread) to another part of the body away from the prostate, such as bone.

Surgical therapy for a more advanced prostate cancer was described as having urologic complications at or above the rates of complication of surgical therapy for early localized prostate cancer: stricture, urinary incontinence, total impotence, and death. Radiation therapy for more advanced prostate cancer was described as having similar urologic complications as surgical therapy—stricture, urinary incontinence, total impotence, and death—with a chance of bowel ulceration and bleeding and a lower chance of immediate death of 0.5% to 1%. Patients were told that with expectant management they would be carefully observed for the development of symptoms

from their prostate cancer with appropriate history, physical examination, blood tests, and studies. Patients were not told explicitly about hormonal therapy as an option in expectant management.

Patients were then asked which treatment (operation or observation) they would prefer if they were the patient in question. They were also asked whether they based their treatment preference on an aspect of the explanation of the two management strategies or on some other information not contained in the questionnaire. Patients who indicated that they based their decision on an aspect of the explanation of either surgical or expectant management were asked to circle those aspects of the explanations that most influenced their decision. Patients who indicated that they based their preference on some other information not contained in the questionnaire were asked to describe the source of the other information. All patients were then given two additional questionnaires: one on sociodemographic items and one on urologic symptoms.

The sociodemographic questionnaire contained the following variables: patient age, level of formal education, and current health status—excellent, very good, good, fair, or poor. The urologic symptoms questionnaire asked a set of "yes" or "no" questions about the following list of urologic symptoms: current ability to achieve and maintain an erection, current difficulty with urination, current urinary dribbling, and current getting up at night to urinate. Patients were also asked ("yes" or "no") whether they had a history of a transurethral resection of the prostate, prostate biopsy, or other prostate-related surgical procedure. To study the influence of these variables on patients' preferences, Fisher's exact test, the *t* test for independent samples, and multiple logistic regression were done.

Results

A total of 140 male patients participated in this study. No patient refused to participate. The mean age of the patients was 66.3 years (standard deviation [SD], 10.35; range, 30 to 82), and the mean level of formal education completed was 12.7 years (SD, 2.73; range, 6 to 22). On the basis of our exclusion criteria, 10 patients were excluded from participating in the study.

TABLE 1.—*Reported Influences on Patient Preferences for Choice of Treatment in Early Prostate Cancer**

Influence	*Surgical Excision n = 74, No. (%)*	*Watchful Waiting n = 59, No. (%)*
Possibility of complete tumor removal	68 (92)	--
Patient experience with previous prostate surgery		
Personal	1 (1)	5 (8)
Family, relative, or friends	4 (5)	5 (8)
Patient's age	1 (1)	1 (2)
Surgical complications	--	47 (80)
Patient's own reading about the 2 treatments	--	1 (2)

*All information obtained from patient self-reports.

Of the 140 patients, 53% (n = 74) preferred surgical therapy; 42% (n = 59) preferred expectant management; 4% (n = 6) reported the desire that their physician make the decision about treatment on their behalf; and 1 patient created his own option and reported that he wanted immediate radiotherapy.

Of the 74 patients who preferred surgical therapy, 68 (92%) reported that their choice was most influenced by the statement in the surgical explanation that "It is possible that all the cancer will be removed." Of the 59 patients who preferred expectant management, 47 (80%) reported that the described surgical complications most influenced their decision in favor of expectant management (Table 1).

Age was significantly ($P < .004$) associated with management choice. Of the 74 patients who selected surgical treatment, 43% (32) were older than 70 years; of the 59 patients who selected watchful waiting, 59% (35) were older than 70 years. The mean age of patients preferring an operation was 63.8 (SD, 11.0) years; the mean age of patients preferring watchful waiting was 69.3 (SD, 8.4) years.

TABLE 2.—*Regression Results in Patients (n = 133) Who Reported Preferring Expectant Management Over Surgical Therapy for Localized Prostate Cancer**

	Multiple Logistic Regression	
Criterion	*Parameter Estimate*	*P Value*
Age, yr†	.074	.002
Formal education, yr	.063	.389
Patient's general health status—excellent, very good, good vs fair or poor	.776	.079
Whether the patient could achieve and maintain an erection	.893	.820
Whether the patient currently had difficulty with urination	.606	.272
Whether the patient currently had urinary dribbling†	.961	.036
Whether the patient currently had to get up at night to urinate	.276	.245
Whether the patient had ever had a TURP, prostatic biopsy, or other operation on the prostate	.143	.756

TURP = transurethral resection of the prostate

*All information obtained from patient self-reports.

†Both increasing age of patients and patients' reports of urinary dribbling were associated with the preferences of expectant management for localized prostate cancer.

Of the urologic symptoms we assessed, only urinary dribbling was significantly ($P < .034$) associated with management choice. Of the 74 patients preferring surgical excision, 16 (22%) reported the presence of urinary dribbling; of the 59 patients preferring watchful waiting, 23 (39%) reported the presence of urinary dribbling.

To study whether patient characteristics were independently related to their expressed preferences, we did an exploratory multiple logistic regression analysis (Table 2). The dependent variable was the patient's preference for surgical therapy or expectant management. Both patient age ($P < .002$) and the presence of urinary dribbling ($P < .036$) had significant independent effects on treatment

choice. The overall relationship of these two variables to treatment choice was modest (estimated $R^2 = .115$, $P = .0002$). Treatment choice was not associated with level of formal education, current health status, or the other urologic symptoms we assessed.

Discussion

Most previous work on patients' preferences has been based on assessing patients' willingness to trade off short-term for long-term survival benefits at five years. In this study, we told patients that research studies on early-stage, low-grade, localized prostate cancer did not indicate any difference in survival at five years or beyond. In this setting of equivalent survival and early localized cancer, we found that most patients still preferred surgical therapy. This majority of patients who preferred an operation reported basing their decision on a phrase used in the study questionnaire: that surgical therapy offered the possibility of complete tumor removal. In our study, we did not ask our patients whether they had a preference for surgery versus expectant management for localized prostate cancer before presenting them with the written scenario and questionnaire. Thus, we cannot say whether patients had preexisting preferences for surgical treatment or expectant management.

The finding of predetermined preferences of patients in favor of surgical intervention for cancer has been reported in studies of women with breast cancer. In one study, 153 women with T1, T2, N1, and N0 breast tumors were asked to choose mastectomy or conservation treatment (excision of the lump, external radiotherapy, and iridium Ir 192 wire implant to tumor bed). Mastectomy was chosen by 99 women.[17] The authors concluded that

> Most women came to their first appointment at the breast clinic already convinced that they had breast cancer, and presumably they had already considered the possibility of mastectomy. When their suspicions were confirmed, one third immediately said that they would have a mastectomy and one third that they would have anything but a mastectomy.[17(p1168)]

The authors point out that one of the salient features of patients' preference for surgical therapy was the fact that the possibility existed that they might still have to have a mastectomy in the future, despite conservative management at the time of their initial decision. Thus, they speculate that what seems to be a simple decision between aggressive and conservative interventions may be influenced by a belief that treatment would be necessary eventually for the disease. Similarly, in our study we cannot say to what extent patients' preferences were influenced by the fact that surgical excision would still be a consideration in the expectant management arm.

Our study is consistent with previous work with breast cancer patients.[17] A substantial number of patients—about a third in the breast cancer study and about half in our localized prostate cancer study—seemed to have a preference for radical surgical treatment of cancer, that is, to have aggressive therapy for breast or prostate cancer right away. In our population of men, however, we cannot say whether this preference existed before their participation in our study. Thus, in comparing these two studies, it appears that a number of older men and younger women may share similar tendencies to favor radical surgery for at least these two types of cancer studied. Future research needs to be done on whether patients have these beliefs about aggressive therapies for cancers in general or whether the beliefs hold only for specific types of cancers.

We found also that older patients and those who reported having urinary dribbling were more likely to prefer expectant management than surgical therapy for localized prostate cancer. We speculate that patients who are already having problems with urinary dribbling were drawn away from the consideration of surgical therapy because of the high rate of occurrence of urinary incontinence as a side effect. Physicians who are eliciting patients' preferences in actual decision making may need to take these factors into account in their discussions with patients.

In summary, our study indicates that patients hold strong beliefs about cancer treatment. Even though we presented patients with information that tended to be biased against prostate surgery (high rates of surgical complications), half of these older male veteran patients still preferred an operation. We did not address the issue of what treatment is most effective for early-stage, low-grade, localized prostate cancer. Rather, our study focused on discovering the preferences patients have that influence their consideration of treatment options. Even though we attempted to bias patients against surgical therapy with the explicit naming of surgical complications and although we gave patients rates of complication occurrence higher than those quoted in the literature, many still preferred surgical treatment of localized prostate cancer. Thus, both urologists and primary care physicians must realize that a substantial number of patients will be coming into such discussions with a tendency to favor an operation. This tendency to favor operative management must be recognized in all studies of how best to discuss treatment choices for localized prostate cancer.

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Articles

Substance-Impaired Physicians
Probationary and Voluntary Treatment Programs Compared

HEIDI D. NELSON, MD, MPH; ANNETTE M. MATTHEWS; DONALD E. GIRARD, MD; *and*
JOSEPH D. BLOOM, MD, *Portland, Oregon*

We compared the characteristics and treatment outcomes of substance-impaired physicians monitored by two different programs in Oregon: a probationary program administered by the Oregon Board of Medical Examiners and the confidential, voluntary Diversion Program for Health Professionals. Demographic, substance use, and treatment outcome variables were obtained by a retrospective medical record review from 41 physicians monitored by the Oregon board and 56 physicians monitored by the diversion program during a 3-year study period. Compared with physicians monitored by the Oregon board, physicians in the diversion program were younger, more likely to be in training programs and less likely to be in hospital-based practice settings, more often reported by immediate rather than third-party contacts, more likely to choose in-state inpatient treatment than out-of-state treatment, and less likely to have concurrent mental illness diagnoses ($P < .05$ for all comparisons). Short-term relapse rates did not differ statistically between the groups (22.0% for the Oregon board group, 14.3% for the diversion program group). The higher number of younger physicians and physicians in training and tendency toward increased reporting by immediate contacts in the diversion program suggested earlier intervention than in the Oregon board group.

(Nelson HD, Matthews AM, Girard DE, Bloom JD: Substance-impaired physicians—Probationary and voluntary treatment programs compared. West J Med 1996; 165:31-36)

Physicians are not immune from the substance abuse problems of current society. Most substance use starts before medical school and reflects drug use patterns of the community.[1] The use of certain substances, such as benzodiazepines and opiates, has an increased onset during residency training due to an increased exposure to the drugs and the attainment of prescribing privileges.[2] The prevalence of alcoholism, the most common addiction of North American physicians, is estimated to be between 7% and 10%, the same as in the United States population.[3] Substance abuse is a major cause of physician impairment.[4]

Impaired physicians often have more difficulty than persons in the general population in seeking treatment.[5] The reasons may include that they tend to deny or fail to recognize their own problems, are more apt to hide difficulties from peers, and often think they can handle their problems themselves. Once in a treatment program, however, physicians have a better prognosis than members of the general population.[5] Most state licensing boards have assumed the responsibility of supervising the evaluation and treatment of substance-impaired physicians, although exactly how this is done varies greatly from state to state.[6-12]

The Oregon Board of Medical Examiners was one of the first medical boards to respond to the American Medical Association's 1972 initiative to develop programs to help impaired physicians.[13] But the program faced early problems when six physicians on probation with the board committed suicide during a 13-month period in 1976 and 1977.[14] In response, beginning in 1977 the board included a psychiatric consultant in all of its deliberations involving impaired physicians.[15,16] Under current procedures, when a physician is reported to the board, an investigation is begun to determine the extent and nature of the problem. If indicated, mandatory inpatient substance abuse treatment is recommended, followed by probation characterized by routine monitoring and often associated with prescribing and license restrictions. All of these activities are reportable to the public. By statute the board has authority to monitor a physician for ten years, although successfully rehabilitated physicians are often monitored for five years.

Beginning in the 1980s, the Oregon Medical Association maintained an informal diversion program, the Physicians' Assistance Committee, for impaired physicians who came to the attention of its substance abuse expert from various referral sources. In 1989 the Oregon Legislature authorized the Oregon Board of Medical Examiners to initiate a formal Diversion Program for

From the Department of Medicine, the Biomedical Information Communication Center, and the Office of the Dean of the School of Medicine, Oregon Health Sciences University, and the Veterans Affairs Medical Center, Portland.

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Reprint requests to Heidi D. Nelson, MD, MPH, Oregon Health Sciences University, BICC-504, 3181 SW Sam Jackson Park Rd, Portland, OR 97201.

Health Professionals, funded by an increase in physician licensing fees, to be operated in a manner semiautonomous from the board. The program began functioning in 1990 by providing substance abuse assessment, intervention, recovery monitoring, and relapse management. Physicians enrolling directly in the diversion program may never make contact with the Oregon board and may never be placed on probation if they demonstrate adequate progress toward recovery. The goals of the diversion program are to encourage earlier intervention by providing confidential, voluntary referral and treatment that results in more effective treatment outcomes.

To determine the status and effectiveness of the diversion program, we compare the differences in characteristics and outcomes of physicians treated in each of these two programs during the first three years of the diversion program's operation.*

Physicians and Methods

The study participants included 97 physicians who participated in monitored treatment of substance abuse with either the Oregon State Board of Medical Examiners or the Oregon State Diversion Program for Health Professionals during the three-year study period from January 1, 1990, to December 31, 1992.

The Oregon board group comprised physicians who came to the attention of the Oregon Board of Medical Examiners because of substance abuse and who received monitored treatment under supervision of the board. Of the 50 physicians who originally presented to the Oregon board, 41 were enrolled in substance treatment programs and monitored by the board and were included in the study. The second group comprised physicians who were evaluated and monitored by the Diversion Program for Health Professionals. Of the 88 physicians who originally presented to the diversion program, 56 were enrolled in the diversion program and were included as study participants (Figure 1). Physicians evaluated but not enrolled were most often found to lack a clear diagnosis of chemical dependency. Physicians in the Oregon board program were enrolled in the study for an average of 27.3 months, a significantly longer period than those in the diversion program, who were enrolled for an average of 18.3 months ($P < .05$).

Data were collected by retrospective medical record review, from the statewide licensing data bank, and from the diversion program inventories and lists. To ensure the confidentiality of the physicians involved in the study, records were identified by code number and reviewed on location at the Oregon board or diversion program offices. Information was abstracted and entered into the computer in coded form by a research assistant so that the identities of participants were never linked to their data sheets nor specified in the analysis. When not in use, the abstraction forms were stored in a locked file cabinet. At no time were the names of any of the participants made available to the Oregon board, the diversion program, reviewers of the article, or all but one of the study investigators themselves. The study was approved by the Human Subjects Review Committee at the Oregon Health Sciences University.

*See also the editorial by J.H. Shore, MD, "Progress in Treatments for Substance-Impaired Physicians," on pages 81-82 of this issue.

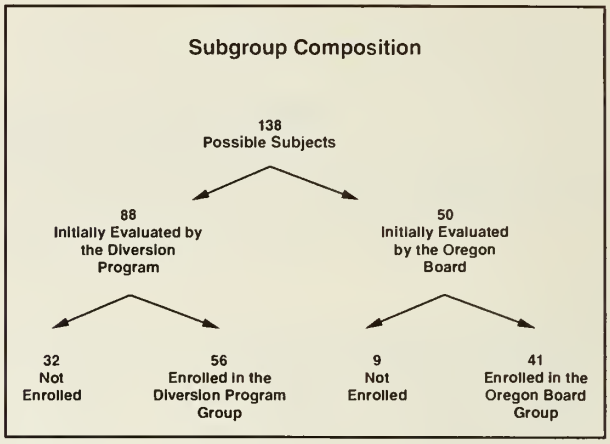

Figure 1.—Study participants were enrolled in the Diversion Program for Health Professionals or the Oregon Board of Medical Examiners program based on their referrals and initial evaluations.

The records contained license printouts, inpatient treatment discharge summaries, continuing care and probation contracts, and quarterly reports of urine monitoring and group therapy. Data were abstracted to a 12-page form that was developed and pretested over a three-month period at the beginning of the study by the investigators and found to be nearly 100% reliable on subsample testing. The variables collected included demographic information, license and education history, dates and method of program entry, drugs of abuse, continuing care and probation details, compliance with after-care monitoring, and early treatment outcomes. These variables were selected because of their importance in addressing the study questions and because they were present in 95% or more of the subjects' charts. Analysis included descriptive statistics, comparison by t tests and χ^2, and the determination of odds ratios and prevalence rates.

Results

There were few statistically significant differences in the general demographic characteristics of the board program's participants compared with physicians in the diversion program, and both groups approximated the demographic characteristics of physicians in Oregon (Table 1). The population was overwhelmingly male (88 [91%]) with a mean age of 45 years; the diversion program group, however, had nine physicians 35 years old or younger compared with one in the board group (16% versus 2%, $P < .05$). All but one physician were white, and 70 (72%) were married. The participants graduated from medical school a mean of 18.9 years ago and had been licensed in Oregon for 14.1 years. They were concentrated in the most populous valley regions of Oregon, with few in coastal or eastern Oregon communities, which are predominantly rural.

Of the 97 physicians, 31 (32%) were in group practice, 22 (23%) in hospital-based practice, 15 (16%) in solo practice, 10 (10%) were interns or residents, and 19

TABLE 1.—*Demographics of Substance-Impaired Physicians in Treatment Programs*

Demographic	Diversion Program*	Oregon Board*	All Oregon Physicians
Number	56	41	7,086
Male, No. (%)	51 (91)	37 (90)	5,895 (83)
Mean age in years (range)	45 (26-70)	46 (34-64)	46.4
Married, No. (%)	38 (68)	32 (78)	N/A
Mean years since medical school (range)	18 (2-46)	20 (7-38)	20
Mean years licensed in Oregon (range)	13 (1-38)	15 (1-36)	15
Trained in Oregon, No. (%)	20 (36)	22 (54)	2,516 (36)
Board certified, No. (%)	38 (68)	24 (58)	4,918 (69)
Location by region, No. (%)			
Coast	5 (9)	8 (20)	N/A
Valley	44 (79)	28 (68)	N/A
East	7 (12)	4 (10)	N/A
Unknown	0 (0)	1 (2)	N/A

N/A = data not available

*No comparisons between study groups are statistically significant at $P < .05$.

(20%) were involved in other practice settings, such as academic, administrative, insurance, and locum tenens. Diversion program participants were significantly more often in training programs as interns and residents and less often involved in hospital-based practice settings than were Oregon board program participants ($P < .05$).

The participants came from most specialty fields. Combined surgical specialties represented the largest group of participants, 57 (59% of total), followed by general internal medicine with 23 (24%) and family practice with 20 (21%). Oregon-adjusted prevalence rates per 1,000 physicians in each specialty were determined using specialty-specific demographic data for the state of Oregon during January 1993, corresponding to the end of the data collection period (Table 2). These prevalence rates are subject to inaccuracy in categories with small numbers, but they provide an adjustment method for comparisons between groups. No significant differences in prevalence rates were found with further grouping of specialties into categories, such as internal medicine versus non–internal medicine specialties, surgical versus nonsurgical specialties, or primary care versus non–primary care specialties. Specialty distributions also did not vary significantly between physicians in the diversion program and the Oregon board group.

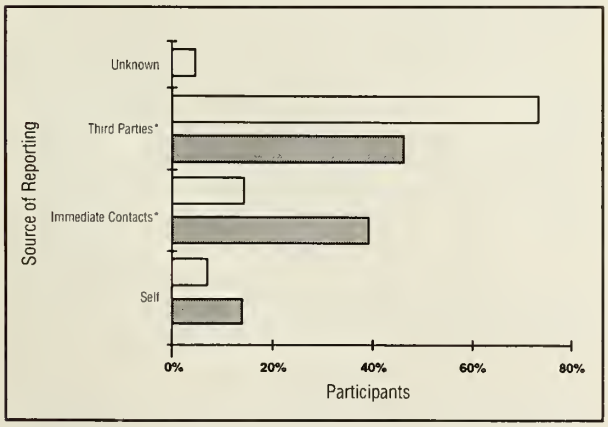

Figure 2.—Participants in the Oregon Board of Medical Examiners program **(white bars)** were more likely to be referred by third parties, whereas those in the Diversion Program for Health Professionals **(shaded bars)** were more likely to be referred by immediate contacts. * = $P < .05$

TABLE 2.—*Prevalence of Physician Impairment in Oregon by Specialty*

Specialty	Physicians, No.	Physicians, % of Sample	Oregon Adjusted Prevalence Rates (per 1,000)*
Internal medicine subspecialties	8	8	61.1
Pathology	4	4	22.5
Emergency medicine	7	7	22.3
General internal medicine	23	24	20.9
Family practice	20	21	15.8
Neurology	2	2	14.9
Anesthesia	6	6	14.9
Surgery	57	59	11.9
Pediatrics	4	4	11.0
Dermatology	1	1	8.9
Obstetrics/gynecology	3	3	8.5
Radiology	1	1	7.2
Psychiatry	2	2	5.2
Unknown	1	1	1.2

*Prevalence rates for groups with small numbers may be inaccurate.

The sources of reporting a physician to the diversion program or the Oregon board differed substantially between programs (Figure 2). Whereas self-referral rates were similar, reports from immediate contacts such as colleagues, patients, friends, and family were significantly more common for physicians referred to the diversion program than those referred to the Oregon board (39% versus 15%, $P < .05$). In contrast, reports from third parties such as insurance companies, police, and review boards were more common for physicians referred to the Oregon board than those referred to the diversion program (73% versus 46%, $P < .05$).

Several types of substances were identified as the predominant drug of use for study participants. Alcohol was most frequently used in both groups of physicians (80% of total), followed by opioids (12%), cocaine and sedatives (both at 3%), and amphetamines and marijuana (both at 1%). There are no statistically significant differences in the distribution of drug use between the two groups. The categories of drugs are combined in Figure 3.

Some aspects of treatment varied between the two groups (Table 3). Significantly more diversion program physicians than Oregon board physicians were treated in Oregon-based inpatient treatment programs (56% versus 70%, $P < .05$). Out-of-state programs in Georgia were the most common alternatives to care in Oregon. The median

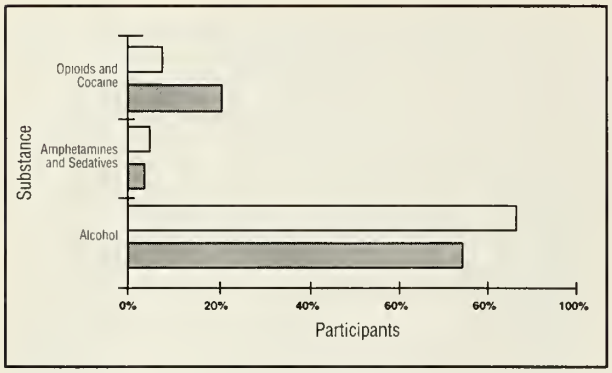

Figure 3.—Substance use preferences were similar for participants in both the Oregon Board of Medical Examiners program (white bars) and the Diversion Program for Health Professionals (shaded bars).

length of stay in inpatient treatment was 30 days for the physicians in the diversion program and 31 days for the Oregon board physicians. A similar number of physicians in both programs had gone through previous substance abuse treatment. More of the Oregon board physicians, however, had concurrent diagnosed mental illness than the diversion program physicians, with depression the most common diagnosis. Relapse rates, as measured by positive random urine drug screens, did not differ significantly between the programs.

Discussion

The results of this retrospective, nonrandomized comparison study indicate that physicians in both programs had similar demographic and professional characteristics and only a small number of differences. Physicians under treatment for substance abuse in the voluntary diversion program were more likely to be referred while younger and in training, tended to be referred by immediate contacts as opposed to third parties, and had short-term relapse rates similar to those of physicians monitored in the probationary state medical board program. These early findings are consistent with the goals of the Oregon Diversion Program for Health Professionals to encourage earlier intervention and effective treatment outcomes.

Identifying and treating physicians earlier in their course of substance abuse may have the greatest effect on outcomes. Our study findings that the diversion program physicians tend to be younger and are more likely in training than board program physicians indicate that residency program directors and colleagues may be less hesitant to refer to the diversion program because of its lack of license sanctions and implications on career development. Although a desirable response, removing the effect of license sanction alone is insufficient for early detection. Substance abuse education programs for medical students, house staff, and practicing physicians are essential for appropriate prevention, detection, and referral. Medical boards, schools, and organizations must assume responsibility for promoting these efforts and ensuring they are effective.

TABLE 3.—*Treatment of Substance-Impaired Physicians in 2 Treatment Programs*

Description	*Diversion Program for Health Professionals n = 56*	*Oregon Board of Medical Examiners n = 41*
Oregon inpatient, No. (%)	39 (70)	23 (56)*
Median length of stay in days (range)	30 (0-102)†	31 (2-113)†
Previous treatment, No. (%)	14 (25)	11 (27)
Mental illness, No. (%)	8 (14)	14 (34)*
Relapse, No. (%)	8 (14)	9 (22)

*The difference is significant at $P < .05$.
†This information is missing for some patients.

The distribution of specialties in the study group appears different from that reported in other studies where anesthesiology, family medicine, surgery, and internal medicine are usually at the top of the list.[5,12,17,18] Although general internal medicine, family medicine, and surgery were the largest groups represented in the study programs, when specialty-specific adjusted prevalence rates were determined, the ranking changed. Specialties with higher-than-expected prevalence rates may need to be examined for risk factors for substance abuse, particularly those that can be modified. Specialty variations may also reflect the small sample sizes of individual studies and need to be interpreted with caution.

Although the average length of stay in inpatient treatment was not significantly different between the groups in our study, 48% of the diversion program and 55% of the Oregon board participants required more than 30 days of inpatient treatment. Most insurance plans do not cover more than 30 days, with coverage estimated at $4,899 to $12,000.[17] Add to this urine specimen testing costs of $28 per test with $13 to $50 collection fees,[17] other associated medical costs, and loss of income, and these treatment costs become substantial, placing tremendous financial burdens on recovering physicians. It is not known to what extent financial costs discourage treatment, nor to what degree medical boards provide financial assistance for rehabilitation. In Oregon, all costs are assumed by the recovering physician.

This study has several limitations. The subjects were not randomly assigned to their groups. Data were obtained by retrospective record review, limiting the type of information available for analysis. Factors other than those obtained in this study could prove useful in determining the selection of physicians for specific treatment programs. The assessment of outcomes was based solely on random urine testing because of the availability of these data. Additional outcomes such as the resumption of medical practice or long-term sobriety may be more accurate measures of the success of a program.

The number of subjects was limited, and they were observed over a relatively short period of time. Women and minorities were underrepresented in the sample and may present different results.[19-21] Although most physician characteristics were similar when comparing diversion program and Oregon board groups, Oregon board participants had significantly more concurrent mental illness di-

TABLE 4.—*Comparison of Impaired Physician Programs*

Study	Program	Physicians, No.	Study Characteristics	Selected Outcomes	Mean Follow-up, yr
Goby et al, 1979[25]	Illinois Lutheran General Hospital	51	1967-1977, record review, survey	56% (24/43) relapse rate	3.5
Kliner et al, 1980[26]	Minnesota Hazelden	85	1973-1976, survey 1 yr after discharge	24% (16/67) relapse rate	1
Johnson and Connelly, 1981[27]	Kansas Menninger Hospital	50*	1974-1979, record review	36% (18/50) relapse rate	0.75-4.5
Herrington et al, 1982[28]	Wisconsin De Paul Hospital	40*	(38 M, 2 F), 1979-1980, record review	83% (33/40) completed program; 33% (13/40) relapse rate	<2
Shore, 1982[11]	Oregon Board of Medical Examiners Rehabilitation Program	27	On probation in 1980, record review	82% (22/27) "improved"; 46% (12/26) relapse rate	3.6
Morse et al, 1984[5]	Minnesota Mayo Clinic	73	67 M, 6 F surveyed in 1978	42% (22/53) relapse rate	3.1
Martin and Talbott, 1987[20]	Georgia Impaired Physicians' Program	37	Female physicians, 1979-1984, interviews	57% (21/37) successful completion; 32% (9/28) relapse rate	N/A
Shore, 1987[12]	Oregon Board of Medical Examiners Rehabilitation Program	49	1977-1985 record review	78% (38/49) "improved"; 57% relapse rate for alcohol; 44% relapse rate for other drugs	6
Geyser, 1988[8]	Board of Medical Examiners of Arizona Rehabilitation Program	49	1980-1985, record review	88% (43/49) "successfully rehabilitated"	N/A
Galanter et al, 1990[24]	Georgia Impaired Physicians' Program	100	100/550 (93 M, 3 F) responding alumni surveys	14% (14/100) relapse rate; 100% (100/100) abstinent at time of survey	2.8
Ikeda and Pelton, 1990[10]	California Physicians' Diversion Program	371	1980-1990, record review	66% (244/371) successful completion	N/A
Pelton and Ikeda, 1991[23]	California Physicians' Diversion Program	51	Anesthesiologists, 1980-1990, record review	69% (35/51) successful completion; 26% (9/35) relapse rate	N/A

N/A = data not available

*Dentists were included.

agnoses, increasing the complexity of their cases and compromising the comparability of the two groups. Despite these shortcomings, the early assessment of new diversion programs is necessary and of interest not only to medical boards and physicians but also to the public.

Although several states have voluntary diversion programs similar to the one in Oregon,[22] no comparative studies have yet been reported. Most of the published literature to date describes individual programs of various types and outcomes of the physicians enrolled in them. Table 4 provides an overview of published results.[5,8,10-12,23-28]

We conclude that a voluntary diversion program for appropriately selected physicians may enhance earlier referral and intervention, resulting in short-term relapse outcomes no worse than for those who enroll in more traditional probationary state medical board programs. The less punitive process of the diversion program may lead to wider use and acceptance and preserve the self-esteem and dignity of impaired physicians. Long-term relapse rates, the maintenance of medical licenses and practices, and other measures of treatment outcomes remain to be demonstrated.

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Articles

Western Impressions of the Hong Kong Health Care System

CHARLES L. BENNETT, MD, PhD, *Chicago, Illinois;*
GLORIA K. PEI, MD, *Hong Kong; and* JOHN E. ULTMANN, MD, *Chicago, Illinois*

Hong Kong, Taiwan, Singapore, and Malaysia are initiating health care reform to meet the changing demands of populations with improved socioeconomic status and access to modern technologies and who are living longer than in previous generations. Hong Kong, in particular, is facing a unique set of circumstances as its people prepare for the transition in 1997 from a British colony to a Special Administrative Region of China. While spending only 4% of its gross domestic product on health care, it has a large and regulated public hospital system for most inpatient medical care and a separate, loosely regulated private health care system for most outpatient medical care. In 1993 the Secretary for Health and Welfare of Hong Kong initiated a year-long process to debate the pros and cons of 5 fundamental programs for health care reform. After a year of open consultation, options were chosen. We describe the Hong Kong health care system, the fundamental changes that have been adopted, and lessons for reformers in the United States.

(Bennett CL, Pei GK, Ultmann JE: Western impressions of the Hong Kong health care system. West J Med 1996; 165: 37-42)

As Hong Kong prepares for the transition from a British colony to a Special Administrative Region of China in 1997, its government has instituted dramatic changes in the structure and financing of health care. While health reformers in the United States look for lessons from European countries and Canada,[1-7] little attention has been paid to Asian countries.

Hong Kong is a territory of 5.9 million inhabitants and an area of 1,076 km^2. Most of its inhabitants (98%) are Chinese.[8] About 3.3 million people live in urban Kowloon and Hong Kong Island, with a population density of more than 40,000 persons per km^2, making it one of the most densely populated areas in the world. In contrast, the remaining population lives in the New Territories, where densities in various districts are frequently in the range of 1,000 to 2,000 persons per km^2. Although a great deal of uncertainty surrounds the changes that will occur after 1997, the existing institutions and social, economic, medical, and educational systems are expected to remain in place (Draft Basic Law of the Hong Kong Special Administrative Region of the People's Republic of China, April 1988).

The per capita health expenditure in Hong Kong in 1991 was HK$3,400 (US$440), substantially lower than that of Japan, the United Kingdom, the United States, and Canada ("Health for All: The Way Ahead," a public consultation document of the Primary Health Care Committee of Hong Kong, 1991). Similarly, the per capita gross domestic product (GDP) of Hong Kong (HK$85,145 [US$10,900 in 1991]) is also substantially lower than that of the other countries. A nearly linear relationship exists between a country's income (as measured by per capita GDP) and health care spending (as measured by per capita health expenditures) across a wide array of nations of different sizes, health care delivery systems, and government types. (The general formula is per capita health GDP = $-290 + [0.1 \times \text{GDP}]$.)[9] Government health expenditure as a percentage of total health expenditures was 61% in Hong Kong, compared with 42% in the United States and 87% in the United Kingdom (Table 1) ("Health for All: The Way Ahead").[6,10]

Despite the relatively low expenditure on health care, health status indicators are better in Hong Kong than in many other countries. In 1991 infant mortality was 5 per 1,000 live births—compared with 10 per 1,000 live births in the United States—and, relative to the United States, life expectancy for Hong Kong adults was two years longer for females and four years longer for males.

Hong Kong's health care system provides general access to medical care and pharmaceuticals, health benefits

From the Department of Health Services Research, the Lakeside Veterans Affairs Medical Center, and the Division of Hematology/Oncology, Northwestern University, Chicago, Illinois (Dr Bennett); the Department of Community Medicine and Unit for Behavioural Sciences, University of Hong Kong (Dr Pei); and the Section of Hematology/Oncology, the Department of Medicine, and the Cancer Research Center of the University of Chicago (Dr Ultmann).

Dr Bennett was a consultant to the Regional Office for the Western Pacific of the World Health Organization when this report was initially prepared. He is the recipient of a Senior Research Associate Career Development Award from the Division of Health Services Research and Development of the Department of Veterans Affairs. The opinions expressed in this report are solely those of the authors and do not represent the views of the World Health Organization, the Hong Kong government, or the Department of Veterans Affairs of the United States.

Reprint requests to Charles L. Bennett, MD, PhD, Dept of Health Services Research, Lakeside Veterans Affairs Medical Center, 333 E Huron St, Chicago, IL 60611.

ABBREVIATIONS USED IN TEXT

GDP = gross domestic product
MRI = magnetic resonance imaging

TABLE 1.—*Government Health Expenditure as Percentage of Total Health Expenditures of Selected Countries**

Country	*Government Health Spending, as % of Total Health Expenditures*
United Kingdom	87
Canada	75
Japan	74
Germany	72
Australia	70
Austria	67
Hong Kong	61
United States	42

*From Schieber et al,[6] the Primary Health Care Committee of Hong Kong, and Cheng and Kwong.[10]

are not linked to employment, out-of-pocket costs are manageable, and there is good access to most preventive and therapeutic services.

Background of the Health Care System

The basic principle of the health care system is that "Hong Kong has a safety net under a 'no turn away' policy, which ensures that no one is denied adequate medical treatment through lack of means. This is the law" (minutes of the Hong Kong Legislative Council, October 13, 1993). Although most of the costs of health care are paid by the government, some costs are borne by the citizens of Hong Kong ("Health for All: The Way Ahead"). For those who cannot afford to pay, the government provides the funds. Health care is not linked to employment, so that workers are free to change jobs without fear of losing access to health care.

The physical aspect of the Hong Kong health care system compares with that of the United States, although human capital is lower (Table 2).[11-13] There are 1.1 physicians per 1,000 Hong Kong residents versus 2.3 per 1,000 in the United States. About 56% of the physicians work in the private sector, where most ambulatory care is provided. Physicians at public hospitals provide most of the inpatient care. Relatively fewer specialists practice in Hong Kong compared with the United States. This difference may increase with the ongoing emigration of physicians who are anticipating political and economic changes in 1997. Although per capita physician visits are about twice as high in Hong Kong, this difference is accounted for by the following factors:

- "Doctor shopping," which is practiced by 46% of the population, whereby more than one physician is consulted for the same illness;
- A low level of diagnostic evaluation;
- A high level of prescribing medications for a few days at a time; and
- Shorter patient visit times—an average of 3 minutes per patient compared with the 10- to 20-minute visits in the United States.

There are about 4.4 acute care beds per 1,000 population in Hong Kong, about the same as in the United States.[14-16] The public hospital system accounts for 89% of the total hospital beds in Hong Kong. Hospital care tends to be overused, with occupancy rates that are considerably higher than in the United States, although hospital stays are shorter. Many hospital admissions in Hong Kong are probably inappropriate by United States standards (Report of the Working Group on Fees and Charges, Hospital Authority of Hong Kong, 1993). Often patients are admitted for nonemergent reasons such as a poor home environment or concern that they will not follow up in general outpatient clinics. Camp beds are used in the corridors of some government hospital wards to handle the overflow number of patients, although recently this has become less frequent.

The public health system has two major branches. The Department of Health oversees the government outpatient departments, communicable diseases, family health, public health, preventive dental care, and planning and development related to health care personnel, health legislation, and supportive services. The other branch, the Hospital Authority, manages the 16 acute care hospitals, 17 extended care facilities, 12 accident and emergency clinics, 4 psychiatric hospitals, and 56 specialty outpatient clinics and is governed by representatives from various sectors of the community (Annual Report of the Hong Kong Department of Health, 1991-1992; Hong Kong Hospital Authority Business Plans, 1991-1992 and 1993-1994).[17,18] Although the Department of Health had a staff of about 6,000 and a budget of HK$1.4 billion (US$179.5 million), the Hospital Authority had a staff of 38,130 and a budget of HK$12.3 billion (US$1.6 billion) for 1993.

TABLE 2.—*Comparison of Health Statistics and Human and Physical Capital Health Statistics Between Hong Kong and the United States*

Statistics	*United States*	*Hong Kong*
Population, in millions (1990)	248.7*	5.9†
Uninsured, %	14.4	0.0
Population ≥65 years of age, %	12.6	8.7
Infant mortality/1,000 births	9.2	6.5
Total physicians/1,000 population	2.3	1.1
Beds/1,000 population	4.3	4.4
Specialist physicians, % of total physicians	42.0‡	33.0
Per capita ambulatory visits, %	5.2§	10.2
Occupancy rates, %		
Nonprofit hospitals	68.0§	84.0
Private hospitals	52.0§	62.0
Average length of stay, days	7.2§	5.5
Days of care/1,000 population	607.0§	1,222.0

*From the US Bureau of the Census.[11]
†From the Annual Report of the Hong Kong Department of Health, 1991/1992, and the Hong Kong Hospital Authority Business Plan, 1993-1994.
‡From the American Medical Association.[12]
§From the National Center for Health Statistics.[13]

The Hong Kong public health system is undergoing many changes (Hong Kong Hospital Authority Business Plans, 1991-1992 and 1993-1994).[18] Long-term care and community service facilities will be promoted. Hospitals will be clustered into eight functional areas to provide vertically integrated care. Specific arrangements will be made for interhospital transfers, networking, and the horizontal integration of specialist services. Hospital budgets will be based not on historical expenditure patterns and bed numbers, but instead will reflect future needs. To increase accountability, each hospital will have a governing committee made up of members from the public and private sectors and a hospital chief executive. Resource consumption profiles will be established, and a prototype specialty costing system will be used for resource allocation purposes. Strategic planning, business planning, explicit statements of roles and responsibilities, performance reviews, communications improvements, and continuous quality improvement are being emphasized by each hospital chief executive.

The private health care system consists of 12 private hospitals and numerous private physicians (Report of the Working Group on Fees and Charges, Hospital Authority of Hong Kong, 1993).[14] The private system is large and provides 20% of the inpatient medical care, 11% of hospital beds, and 70% of the outpatient visits and is staffed by 3,424 private practice physicians (compared with 2,819 in the public health system). Patients generally seek private outpatient medical care by self-referral.

Private hospitals charge a basic fee for inpatient room services. Physicians are paid fees for service and have no financial incentive to shorten the duration of hospital stays or to limit the number of diagnostic tests or treatments. Medical resources and physician fees are charged separately, with the charge for each item varying according to the class of patient. Patients are required to pay a deposit before admission, and patients with long stays are usually asked to settle their bills every five days.

Physicians in the private sector believe staunchly in a free market for health care, and 95% operate solo practices. There is extensive price discrimination in the private sector. The same physician may charge 2 to 20 times for a first-class patient as for a third-class patient.[15] (The class of a patient is determined by the type of room service received—private room [first class], semiprivate [second class], and ward [third class]). A report by the Medical Insurance Association of Hong Kong identified twofold differences in charges among private physicians for several diagnostic tests and operations.[15] The fee structure is rather loose, and negotiations are often carried out in a way that would be unsettling to western cultures. Many patients receive medical care in the private sector without knowledge of the physician's fee scale; an increasing number of patients, however, are attempting to agree on the fees before seeing the physician. Physician fees are usually paid at the time of service, with less than 10% of fees being paid directly by insurance companies.

Financing and Expenditures

Hong Kong financing for health care is based on shared fiscal responsibility by the government and the people, rather than private insurance companies. There are three sources of funds: general taxation, insurance, and out-of-pocket payments. The private insurance sector is underdeveloped. Taxes account for 43% of the health expenditure, and out-of-pocket payments account for 57%.[19] The maximum personal income tax rate is limited to 15% of gross income before deductions for allowances. Persons in business or professional services pay taxes on profits at a rate of 17.5% for corporations and 15% for other persons. Property tax is charged at a standard rate of 15% on the annual rent received, less a statutory deduction of 20% for repairs and outgoing expenses. (Hong Kong Government Information Services: Hong Kong, 1991—A Review of 1990).

Inpatient public services are charged to patients at HK$43 per day (US$6), whereas the average operating cost is HK$2,105 per day (US$270) ("Towards Better Health," a consultation document of Hong Kong, 1993). (Based on the differences in per capita expenditure between the United States and Hong Kong, the cost of admission to a public hospital in Hong Kong would be comparable to about a $US15 out-of-pocket daily expenditure for a similar intensity of care in a public hospital in the United States.) Outpatient clinic fees are HK$21 per day (US$3) for all medical care, tests, and pharmaceuticals—compared with an average private general practitioner fee of HK$100 (US$13)—whereas average outpatient costs are HK$111 per day (US$14). Treatment at public accident and emergency departments is free, and average costs are HK$428 per patient (US$55).

Hong Kong, like the United States, is facing changes in its society that require increased health care expenditures (Report of the Working Group on Fees and Charges, Hospital Authority of Hong Kong, 1993; "Towards Better Health," Hong Kong, 1993).[8] Its population is aging, medical costs are rising, new medical technologies are being developed, and community expectations are increasing. The annual per capita out-of-pocket expenditure is HK$1,745 (US$223), with widespread variation due to the frequent use of unregulated traditional Chinese medical care, large variations in the use of services according to socioeconomic class, and differences in medical fees according to socioeconomic status.[20] The recent increase in health expenditures is substantial. Total health expenditures have increased by 44% in 1991 over the previous two years, and the government expenditure for public clinics, hospitals, and other government facilities increased by 65% over the same period.[20] Although some of the increase in expenditures is accounted for by inflation, most of the change has been due to the rapid increase in the GDP (>8% per year) and the stable population size, which has resulted in an accumulation of government funds for health and other public goods. The Governor of Hong Kong has predicted a 22% increase in real expenditure on health care over the next five years.

Although 90% of private medical care is paid for by patients' out-of-pocket funds, only 14% of the population has private medical insurance. The private insurance sector has been growing at a rate of 40% per year, with the highest rate of insurance coverage (23%) being among young adults aged 20 to 39 years whose policies are provided by large multinational corporations.[14]

Provider Payments

Salaries differ greatly between the public and private sector physicians. In the past, Hospital Authority physicians were employed as civil servants and received a fixed salary and benefits for housing, leave, and education. More recently, these physicians have been hired outside of the civil service category with an average income that has risen to the range of HK$1 million (US$128,000) to make up for the discontinuation of the housing allowance. The salaries of private physicians are substantially higher, but vary considerably, depending on the socioeconomic status of their patients and the degree of competition from other physicians. A survey in 1990 found that general practitioners charged a median fee of HK$100 (US$13) per consultation and HK$650 ($83) for first-class patients, whereas specialists charged from HK$200 to $300 (US$26 to $39) for clinic patients and HK$800 (US$104) for first-class patients. Fees for major operations ranged from HK$9,000 to $40,000 (US$1,153 to $5,128), with a median of HK$20,000 (US$2,564).[14] Physicians make a substantial profit from dispensing pharmaceuticals, often recalling patients for a second visit in one to two days to renew a prescription while collecting consultation and pharmacy charges.

Technology

The diffusion of new technologies in Hong Kong lags behind that in the United States. Because of the regionalization of medical services, there are often queues for the use of the latest technologies in the public hospitals. Patients may be asked to purchase expensive equipment such as prosthetic hips, cardiac catheterization equipment, or cardiac pacemakers. In the past, magnetic resonance imaging (MRI) has been difficult to obtain at public hospitals because there was only one MRI scanner. Inpatients at public hospitals were often encouraged to pay for an MRI at a private hospital and return after the scan was done. With the purchase of two more scanners, this problem is expected to be alleviated.

It is difficult to obtain some diagnostic tests and treatments because of limited equipment in public clinics. X-rays are not always available, but the use of electrocardiograms is becoming widespread. In contrast, diagnostic tests are readily available for patients who can afford private health care at any one of the 12 private hospitals or in private physician offices.

Access to Health Care

Government outpatient departments are crowded. Queues begin to form one to two hours before a clinic opens, and appointments are given for as many as 80 patients per physician per half-day. After the daily quota of appointments is given out, no further appointments are taken. Because physicians see a large volume of patients, there is little time to communicate with patients and even less for counseling, reassurance, and education.[16,21,22]

Emergency care is a basic right of all Hong Kong and British residents. Because of free care at emergency departments and substantial queuing at outpatient clinics, emergency departments are often used inappropriately for nonemergent and routine ambulatory care.

Reform: Five Options

Health care reform has been identified as an important task to be tackled before 1997. The Secretary for Health and Welfare, Elizabeth Wong, in a statement for the Hong Kong Legislative Council in October 1993 summarized this need:

> While we have a good health system with a "no turn away" policy, which provides guaranteed coverage for all, we still need to reform the structure to make it better. Thus, the consultation document [on health reform options] is not about fee increase, but is about structural change. The health of our community is of paramount importance: we cannot leave its future to chance. Between chance and change, there is really very little choice. With new technology, rising expectations, health care is expensive business. It is everybody's business.

Hong Kong has concluded a year-long debate process on health care reform. In early 1993, Mrs Wong called for open public commentary on the five possible options for reform listed in the consultation document ("Towards Better Health"). The following options were proposed.

Option A

Patients would be asked to pay a fixed percentage of the overall operating cost for an inpatient stay. Cost recovery percentages that have been suggested range from 5% to 15%, whereas currently greater than 95% of the costs are subsidized by the government. A waiver system would be maintained in this option to be applied to all cases with financial hardship.

Option B

This option comprises three major elements: semiprivate rooms in public hospitals that would be available for a flat rate of 40% to 60% of the daily operating cost; itemized charges for a hospital admission, first visit to a specialty clinic, pharmaceuticals at a specialty clinic, and the use of accident and emergency services; and waivers for public assistance recipients, persons with disability, and those 70 years of age and older, unemployed, or chronically ill.

Option C

A coordinated voluntary insurance plan is proposed in which private insurance companies compete with each other for subscribers. The insurance policies will be evaluated by a central clearing body.

Option D

A compulsory comprehensive insurance approach is administered either by the government or a separate statu-

TABLE 3.—*Summary of Public Views on Health Care Reform*†*

		Option						
		A	B			C	D	E
Groups	Submissions, No.	Percentage Subsidy	Semiprivate Rooms	Itemized Charges	Target Waiver Groups	Coordinated Voluntary Insurance	Compulsory Insurance	Oregon Approach
Individuals	195	− − −	+ + +	− − −	+ + +	+ + +	− −	− − −
Health care professionals	45	+ +	+ +	+	+ + +	+ + +	− − −	− − −
Organizations	83	− − −	+	− − −	+	+	− −	− − −
District boards	19	− − −	+	− − −	− −	− −	− − −	− − −
Others	53	− − −	− − −	− − −	− − −	− − −	− − −	− − −

*From a statistical analysis of health care reform options, a public document distributed by the Secretary for Health and Welfare of Hong Kong. "Organizations" mostly consisted of social services centers and centers for the elderly. "Others" include signature campaigns, survey reports, and statements of political parties.

†Key: + + + = support:oppose ratio > 4:1
+ + = support:oppose ratio > 2:1
+ = support:oppose ratio > 1:1
− − = oppose:support ratio > 2:1
− − − = oppose:support ratio > 4:1

tory body. Premiums would be either the same rate for everyone or vary according to age and risk; employers or subscribers might pay the premium.

Option E

The treatment approach will be systematically rated, analogous to the plan recently developed in Oregon in the United States whereby medical resources would be allocated according to diagnoses that have been organized by their level of severity.

The five options were published in 1993 in a government consultation document, "Towards Better Health," and public comment was requested. More than 300 written responses were received by September 30, 1993, when the official consultation period ended. The Legislative Council of Hong Kong debated health care reform in October 1993, which led to the submission of almost 200 more responses. The responses indicated that health care reform was viewed differently by the various sectors (Table 3). In general, seven groups—individuals, health professionals, social organizations, district medical boards, signature campaigns, survey reports, and political parties—voiced their opinions. Most supported option B (establishing semiprivate rooms and identifying target waiver groups) or option C (introducing a voluntary coordinated insurance program).

In late 1993, a decision was made by the Executive Council of Hong Kong in support of a combination of the target group approach and coordinated voluntary insurance (options B and C), choices favored by most political parties, public organizations, and the government.

Several consequences of the new policies have been considered by policy makers. At least half of the funds that will be raised through option B will be retained by the Hospital Authority. The Executive Council of Hong Kong also approved the formation of an internal assessment committee under the leadership of the Secretary for Health and Welfare to formulate proposals on the appropriate level of cost recovery for public beds in Hospital Authority hospitals. Finally, an implementation strategy committee made up of health care experts and community representatives will monitor the implementation of options B and C and ensure that there is good feedback from the community (Elizabeth Wong, Secretary for Health and Welfare, written communication, January 1994).

Lessons Relevant to the United States

The Hong Kong health care system is a good example of a health care system in a newly industrialized country that provides for basic medical needs. The system generally provides good access to medical care in which new technologic advances are minimal, private sector options are not dominated by policies of large insurance companies, and health care costs are only 4% of the GDP. The emphasis is on affordability while maintaining the workings of the free-market economy. A tax-based, rather than employer-based, financing system provides for universal comprehensive coverage with financial protection against the high costs of illness while preserving the ability of workers to change jobs without losing health benefits. By maintaining health expenditures at 4% of GDP, other parts of the economy are able to grow. The Hong Kong system has the workings of the free-market economy of Hong Kong with features such as minimal burdens of utilization review, low malpractice costs, and low administrative costs. The introduction of user fees for clinics, medications, and accident and emergency services, however, as well as the development of a private health insurance system will adversely affect access. To make substantial changes in health care financing that will not benefit all, extensive public involvement was consulted. Options were outlined publicly, public opinion was sought, and finally, a consensus was achieved.

The Hong Kong free-market approach to health care is based on rational expectations, in that those citizens who want nicer rooms and other amenities must pay for these items. Health reformers in other countries would be wise to consider similar strategies. As in the United States, patients who value out-of-system options are asked to pay an additional cost for this care, but these medical care options are not dominated by large private insurance plans.

The major lesson from the Hong Kong experience is in the process of health care reform, rather than the actual health care system. In the United States, policy makers are actively pursuing cutbacks in health care financing in a debate marked by confrontation among political groups, lobbyists, and constituents, whereas health care reform in Hong Kong was based on collaboration among the various parties who participated in extensive rounds of consultation and debate.

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Conferences and Reviews

Cervical Spondylosis
An Update

BRUCE M. McCORMACK, MD, *and* PHILLIP R. WEINSTEIN, MD, *San Francisco, California*

Cervical spondylosis is caused by degenerative disc disease and usually produces intermittent neck pain in middle-aged and elderly patients. This pain usually responds to activity modification, neck immobilization, isometric exercises, and medication. Neurologic symptoms occur infrequently, usually in patients with congenital spinal stenosis. For these patients, magnetic resonance imaging is the preferred initial diagnostic study. Because involvement of neurologic structures on imaging studies may be asymptomatic, consultation with a neurologist is advised to rule out other neurologic diseases. In most cases of spondylotic radiculopathy, the results of conservative treatment are so favorable that surgical intervention is not considered unless pain persists or unless there is progressive neurologic deficit. If indicated, a surgical procedure may be done through the anterior or posterior cervical spine; results are gratifying, with long-term improvement in 70% to 80% of patients. Cervical spondylotic myelopathy is the most serious and disabling condition of this disease. Because many patients have nonprogressive minor impairment, neck immobilization is a reasonable treatment in patients presenting with minor neurologic findings or in whom an operation is contraindicated. This simple remedy will result in improvement in 30% to 50% of patients. Surgical intervention is indicated for patients presenting with severe or progressive neurologic deficits. Anterior cervical approaches are generally preferred, although there are still indications for laminectomy. Surgical results are modest, with good initial results expected in about 70% of patients. Functional outcome noticeably declines with long-term follow-up, which raises the question of whether, and how much, surgical treatment affects the natural course of the disease. Prospective randomized studies are needed to answer these questions.

(McCormack BM, Weinstein PR: Cervical spondylosis—An update. West J Med 1996; 165:43-51)

Clumsy hands and the wide-based, stooped, somewhat jerky gait of elderly persons have been described throughout the ages. Likewise, neck and upper extremity pain is such a ubiquitous ailment of aging that "pain in the neck" has entered our language as a figure of speech. It was not until 1952, however, that it was recognized that the myelopathy and radiculopathy from cervical spondylosis constituted clinical disorders.[1] Degenerative disease of the cervical spine and its cartilaginous and ligamentous structures is known to be the most common cause of cervical cord and root dysfunction in patients older than 55 years.[2] Pathogenic mechanisms have been better defined,[3-5] in part, through advances in neuroimaging, such as magnetic resonance (MR) imaging, which has also simplified diagnosis and facilitated treatment.[6-10]

Treatment was largely supportive until 1892 when Victor Horsely performed a cervical laminectomy for a patient with spondylotic myelopathy.[11] Anterior cervical spine approaches were developed in the 1950s as the mechanism of disease and the pathophysiology of radiculopathy and myelopathy were better defined.[12,13] In the 1970s, the use of the operating microscope and microsurgical techniques for cervical spine surgery was popularized.[14,15] More recently, spinal instrumentation developed for the treatment of traumatic instability[16-18] has been used in patients with cervical spondylosis to do radical decompressions, provide spinal stability, and enhance bone healing.[19]

In this article, we summarize the salient features related to the pathogenesis, clinical diagnosis, and treatment of cervical spondylosis.

Pathophysiology

Cervical spondylosis is caused by a degeneration of the intervertebral discs, which fragment, lose water content, and collapse with normal aging.[20,21] Disc degeneration causes increased mechanical stress at the cartilaginous end plates at the vertebral body lip. This results in subperiosteal bone formation or osteophytic bars that extend along the ventral aspect of the spinal canal and, in some cases, encroach on nervous tissue. Osteophytes or "hard disc disease" should be differentiated from soft disc herniations of fibrocartilage that occur in young and middle-aged adults.[1] Spondylotic changes in the cervical spine occur at solitary disc space levels in 15% to 40% of patients and at multiple levels in 60% to 85%.[1,22] The discs

From the Department of Neurological Surgery, University of California, San Francisco, School of Medicine, and the Veterans Affairs Medical Center, San Francisco.
Reprint requests to Bruce M. McCormack, MD, Veterans Affairs Medical Center, Dept of Neurological Surgery (Box 112), 4150 Clement St, San Francisco, CA 94121.

ABBREVIATIONS USED IN TEXT

CT = computed tomography
EMG = electromyography
MR = magnetic resonance

between the third and seventh cervical vertebrae are affected most commonly.

Repeated occupational trauma may contribute to the development of cervical spondylosis.[1,23,24] An increased incidence has been noted in patients who carried heavy loads on their heads or shoulders, dancers, gymnasts, and in patients with spasmodic torticollis.[22] Not everyone agrees that trauma is an important causal factor in the production of this disorder.[1] In about 10% of patients, cervical spondylosis is due to congenital bony anomalies—blocked vertebrae, malformed laminae—that place undue stress on adjacent intervertebral discs.[1,22]

Cervical spondylosis may result in symptomatic spinal cord compression.[1,20-22] The presence of a congenitally narrow spinal canal—diameter of 10 to 13 mm—is a critical predisposing factor in patients with spondylotic myelopathy.[3,5,25-29] Congenital spinal stenosis is poorly understood and occurs sporadically, within families, and in achondroplastic dwarfs.[30] Symptomatic cord compression occurs as degenerative spinal changes result in further narrowing of a developmentally narrow spinal canal. Degenerative stenosis is usually caused by ventral spondylotic bars. The thickening of bone and ligaments of the spinal column, laminar "shingling," and ligamentum flavum buckling into the posterior spinal canal also contribute to spinal stenosis. Pathologic vertebral body subluxations may further narrow the sagittal diameter of the canal. Other mechanisms, aside from static cord compression, have been implicated in the pathophysiology of cervical spondylotic myelopathy.[3-5] Cervical motion causes chronic cumulative cord trauma from impaction of the spinal cord against bony spurs or from pathologic subluxation of vertebral bodies. Acute spinal cord injury may occur from neck extension when the cord is pinched between anterior osteophytes and an infolding ligamentum posteriorly. Neural ischemia from repetitive minor contusion due to trauma and vascular compromise due to stenosis are also thought to be contributory.

The spinal cords of patients with cervical spondylotic myelopathy are flattened at the levels of spondylotic protrusions.[31,32] At the level of compression, the gray matter is ischemic, with a loss of neurons and, in some cases, cavitary lesions. There is degeneration of the lateral descending columns below the level of compression; ascending posterior columns degenerate above the compressed level. White matter lesions include irregular areas of pallor, necrosis, and demyelination.

Cervical spondylotic radiculopathy is caused by nerve root compression in the neural foramina.[33-35] The root normally occupies about a third of the space in the foramen and is accompanied by radicular arteries and veins. The root is vulnerable to compression by the facet joint posteriorly or the uncovertebral joints and disc anteriorly. The facet and uncovertebral joints may hypertrophy, or the disc may rupture or become calcified. It is conjectured that nerve root irritation may also occur from a degradation of discal proteoglycans without direct compression.[36] Nerve roots in patients with spondylotic radiculopathy are flattened, with surrounding fibrosis of the root sleeve. Wallerian degeneration is uncommon.[1]

Clinical Spectrum and Natural History

Cervical spondylosis occurs in middle-aged or elderly patients. It may cause neck pain syndromes, myelopathy, or radiculopathy.[1-3,25,34,35,37] Neck pain and stiffness with radiation into the shoulders or occiput may be chronic or episodic with prolonged periods of remission. Flexion-extension injuries, blows to the head, or neck injury while lifting heavy objects may precipitate an acute exacerbation. Neck pain usually accompanies upper extremity radicular symptoms and often may be absent in patients with myelopathy.[1,22,38-41] Abnormal findings of an examination consist of decreased mobility, muscle spasms, and tenderness.

Radicular and myelopathic symptoms are usually distinct syndromes with little overlap.[42] There are fewer cases of myeloradiculopathy in which signs of nerve root dysfunction in the upper limbs accompany long tract signs in the lower limbs. In these patients, it is difficult to know for certain whether to ascribe findings in the upper limbs to a lesion of the nerve roots or to one of the corresponding segments of the spinal cord. Some think that myeloradiculopathy is the most common neurologic presentation of cervical spondylosis.[22,27]

Myelopathy

Myelopathy due to cervical spondylosis usually develops insidiously, although episodes of abrupt deterioration occur.[2,21,22,43] Acute spinal cord injury may rarely occur in elderly patients after traumatic cervical spine hyperextension.[44] The syndrome of "numb, clumsy hands" has been described in patients with high compressive myelopathy between C-3 and C-5. Typical symptoms are loss of manual dexterity, with difficulty writing; diffuse, nonspecific arm weakness; and abnormal sensations.[45,46] Lesions at levels C-5 to C-8 cause a syndrome of spasticity and proprioceptive loss in the legs. Patients have difficulty walking and an unsteady feeling; they often lose their balance and fall. Urinary frequency and urgency are common. A complete loss of bowel and bladder function is an end-stage deficit that is rare.

Neck flexion and extension may elicit electric shock sensations in the extremities (Lhermitte's sign). There is motor weakness, sensory loss, and spasticity with exaggerated reflexes below the level of spinal cord compression. Extensor plantar responses are elicited. Myelopathic syndromes may localize asymmetrically to one side of the body (Brown-Séquard syndrome). The deficit may affect predominantly motor function with preserved sensation (anterior cord syndrome) or cause hand weakness proportionally greater than leg weakness (central cord syndrome). Neurologic deficits have been graded on the basis

of gait[47]; effects on activities of daily living[48]; or motor, sensory, and bowel function.[49]

The natural history of cervical spondylotic myelopathy is variable, with some patients having a mild protracted course and others progressive disability.[22,28,39,47,50,51] In a report on 26 untreated patients, motor deficits were found to have developed over time without complete remission.[22] In 19 patients, myelopathy progressed episodically, usually with ongoing deterioration between episodes. In 5 patients, there was slow, steady progression without remission phases from the onset onward, whereas in 1 there was a rapid onset followed by lengthy periods of stability. In a review of 44 patients who had myelopathy on initial presentation, the course of the disease was noted to be "benign," with long periods of nonprogressive disability the rule and a progressively deteriorating course the exception.[39] Those who disagree with these conclusions observed that 25 of the patients in that study (57%) had severe disability at some time, and in most this remained[51]; only 8 patients (18%) improved based on the disability category.[28] In 1967 a report of the experience of 48 patients found a less favorable natural history, with 32 patients having a steadily progressive deterioration.[28] In a review of the literature, it was found that 30% to 50% of patients with myelopathy improved with nonoperative treatment.[50]

Radiculopathy

Radiculopathies develop insidiously or may be triggered by trauma.* Because more than one cervical spine segment is often affected, symptoms are more diffuse than those associated with unilateral soft disc herniation, and they may be bilateral. Acute neck and arm pain, paresthesias, and weakness are typical, but one condition may exist without the others. Less commonly, the pain may radiate to the chest or face. On examination, sensory loss, weakness, and hyporeflexia may be seen in a radicular pattern. In advanced cases, muscle wasting and fasciculations may occur. The C-6 and C-7 roots are the most commonly affected.[34,40,52,53,55] The Spurling maneuver may be done to elicit radicular symptoms. It is performed by extending the patient's neck, rotating the patient's head to the side of the pain, and then applying downward pressure on the head.[56]

A recent epidemiologic survey of cervical radiculopathy indicates that symptoms resolve in 75% of patients with conservative measures.[53] A fifth of the patients in that survey were treated surgically. At six years' follow-up, 90% of patients were asymptomatic or only mildly incapacitated. Disparate outcomes for conservative management of cervical radiculopathy have been reported. Referral center-based studies indicate persistent pain and incapacity in two thirds of patients treated conservatively.[33,39] Surgery-based studies indicate that complete relief with nonoperative therapy occurs in only 29% of patients.[57] Another study found that 23% of patients remain partially or totally disabled.[58] Physiotherapy centers find, however, that 70% to 92% of patients have good relief with physiotherapy and cervical traction.[54,55,59,60]

*References 1, 22, 33-36, 38, 40, 42, and 52-54.

Differential Diagnosis

Cervical spondylosis is ubiquitous in elderly persons, and neurologic dysfunction may or may not be attributable to spondylotic cervical spine changes seen on imaging studies.[6,61] Misdiagnosis is a well-recognized cause of a poor surgical outcome.[62] Neurologic consultation is advised to interpret clinical findings and obtain radiologic and electrophysiologic tests.

The following diseases should be considered in the differential diagnosis of cervical spondylosis with myelopathy or myeloradiculopathy: motor neuron disease, multiple sclerosis, spinal cord tumor, syringomyelia, and tropical spastic paraplegia.[62,63] Spinal cord tumor and syringomyelia are readily diagnosed with MR imaging. Tropical spastic paraplegia is attributable to human T-lymphotropic virus type I and occurs in patients from the Caribbean region and in patients infected through blood transfusions.

It may be difficult to differentiate between cervical spondylotic myeloradiculopathy and motor neuron disease. Both conditions tend to appear in older patients. The diagnosis of motor neuron disease should be favored if sensation is normal or if muscular fasciculations are present in the tongue, face, or lower extremities.[62,63] The clinical diagnosis is supported by typical findings on electromyography (EMG): substantially longer duration of the motor unit potentials combined with signs of denervation, such as fibrillations, sharp positive waves, and fasciculations.

The spinal form of multiple sclerosis may mimic the clinical course of cervical spondylotic myelopathy and radiculopathy.[34,62,63] Patients with cervical myelopathy are usually older, oligoclonal bands in the cerebrospinal fluid are absent, and the visual evoked potentials are normal. Magnetic resonance imaging may detect demyelinating plaques in patients with multiple sclerosis, but white matter lesions, probably vascular in origin, are frequently seen in patients older than 50.

The differential diagnosis for cervical radiculopathy includes upper limb nerve entrapment syndromes and brachial neuritis (neuralgic shoulder amyotrophy).[34,63] The carpal tunnel syndrome and ulnar neuropathy may be differentiated from radiculopathy because symptoms are in the distribution of a single peripheral nerve whereas multiple nerves are involved with radiculopathy. Median neuropathy at the wrist, however, may present with proximal symptoms as high as the neck. Tinel's sign, which consists of radiating paresthesia in the distribution of a peripheral nerve when the nerve is tapped with a finger, is often present with nerve entrapment. In some patients, the diseases may coexist, referred to as the double-crush syndrome.[64,65] The syndrome occurs from the proximal compression of the nerve root at the neural foramen, which weakens the nerve's ability to withstand distal compression at the wrist or elbow. Electromyography will distinguish between an entrapment syndrome and radiculopathy and, if they are both present, define the distribution of abnormalities.

Acute brachial radiculitis refers to acute shoulder and neck pain followed by weakness and atrophy of the shoul-

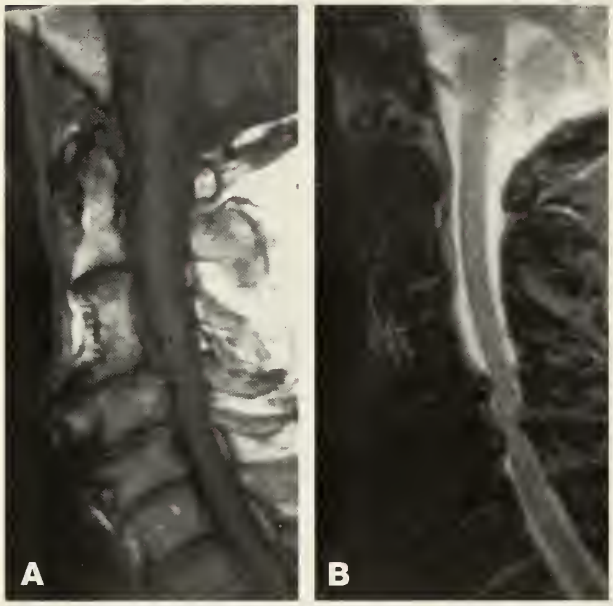

Figure 1.—**A,** A sagittal T1-weighted magnetic resonance (MR) image of the cervical spine in a patient with myelopathy shows detailed gross anatomy. Cord compression is seen at C3-4 and C4-5. **B,** Spin echo or gradient echo T2-weighted MR images provide a "central nervous system myelographic" effect to highlight anterior cord compression. Increased signal intensity in the cord on this T2-weighted image indicates cord damage and may be a poor prognostic sign.

der girdle and the upper limb muscles due to an inflammatory allergy. Symptoms are bilateral in 25% of cases.[63,66-68] The syndrome may be differentiated from cervical spondylotic radiculopathy by the high intensity of the pain followed by weakness, after which the pain usually recedes, the absence of a Spurling's sign, normal findings on a cervical paraspinal EMG examination, and imaging studies that do not show a lesion sufficient to result in a severe neurologic deficit.

Other diseases may affect the cervical spine and cause spinal cord or root impingement. Rheumatoid arthritis affects the cervical spine in 36% to 88% of cases.[69] Myelopathy may result from basilar invagination, C1-2 subluxation, and spondylolisthesis of other cervical vertebrae. Radiculopathy may result from osteoarthritis of intervertebral and uncovertebral joints. Ossification of the posterior longitudinal ligament, ankylosing spondylitis, and diffuse idiopathic skeletal hyperostosis are arthritic conditions that may result in neurologic manifestations identical to cervical spondylosis.[70]

Imaging Studies

Plain radiographs are an inexpensive initial diagnostic study. They are of limited specificity because degenerative changes are present in both symptomatic and asymptomatic patients.[61] A loss of disc space height and osteophyte formation with narrowing of the sagittal canal diameter are visualized on the lateral projection. A narrow spinal canal, with a sagittal diameter of 10 to 13 mm, has been associated with a higher incidence of neurologic deficits,[5,25-29] but this measurement is less important with the introduction of MR imaging, which directly visualizes neural structures. Neural foraminal narrowing is seen on oblique views. Plain radiographs are helpful in assessing spinal alignment and the contribution of degenerative spondylolisthesis—relative displacement of one vertebral body to another—to canal stenosis. Cervical spine flexion and extension views are used to assess spinal stability.

Magnetic resonance imaging is the preferred initial imaging study (Figures 1 and 2).[71-73] In one study, MR imaging correctly identified 88% of the surgically proved lesions, compared with 81% for postmyelographic computed tomography (CT), 58% for myelography, and 50% for CT.[72] Advantages include the lack of irradiation, the avoidance of invasive intrathecal contrast administration, and the capability of multiplanar imaging.[71] In addition to its greater sensitivity in the detection of disc disease and extradural compression, MR imaging also better displays

Figure 2.—A sagittal T2-weighted magnetic resonance image is shown of a patient with myelopathy. The spinal canal is developmentally narrow with cord compression at every level. This patient was treated with laminectomy.

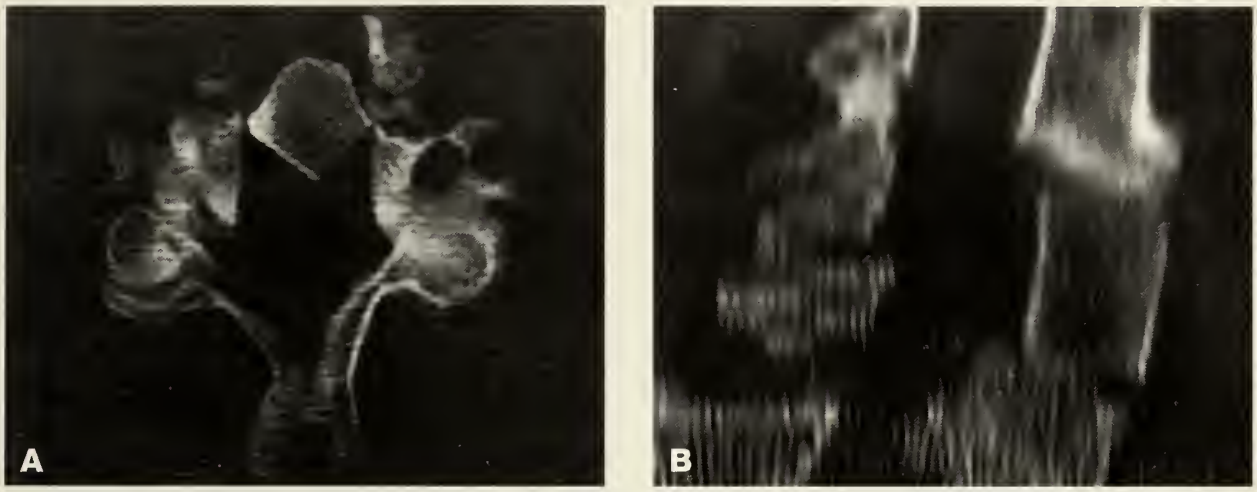

Figure 3.—**A,** A computed tomographic (CT) scan with sagittal reconstruction is shown in the same patient as in Figure 1 after C-4 vertebrectomy. **B,** An axial CT scan shows wide decompression of the canal with a bone plug in good position. Note the exuberant bony overgrowth of anterior osteophytes.

intramedullary cord disease.[7] A limitation of MR imaging is that it may not provide enough bone detail.[71] Cervical MR imaging is also subject to more artifact and distortion than is lumbar MR imaging.

Computed tomography after the introduction of water-soluble contrast agents is an alternative accurate method for evaluating patients with neurologic symptoms.[71] Many surgeons prefer CT myelography for the evaluation of radiculopathy because CT provides superior imaging of bone compared with MR imaging and better defines the anatomy of the neural foramina. Computed tomography is often used to complement MR imaging to provide additional bony detail to characterize the lesion responsible for neural entrapment (Figure 3).[72]

Treatment

The treatment of cervical spondylosis may be medical or surgical, depending on whether a patient presents with symptoms of myelopathy, radicular pain, or neck pain. These clinical symptoms overlap, but are discussed separately for clarity.

Myelopathy

Patients presenting with mild myelopathic symptoms may be treated conservatively and observed over time because many such patients have a protracted course of minor impairments without progression.[22,39,47,50] The cornerstone of conservative therapy is to immobilize the cervical spine with a collar that holds the head in a neutral or slightly flexed position.

Surgical treatment is recommended for patients with moderate or severe disability when first seen because conservative therapy yields an improvement rate of only 30% to 50% of such patients.[50] The effects of surgical treatment on the natural history of spondylotic myelopathy have been questioned,[39,41,62,74] and prospective, randomized studies have been proposed to clarify the role of surgical therapy.[41,62,75] Despite some controversy, the bulk of evidence suggests that patients with moderate to severe symptoms of myelopathy are best treated surgically. Several clinical and radiologic criteria have been recognized as possible predictors of outcome, including abnormal spinal cord signals on MR imaging that may portend a poor prognosis (see Figure 1-B).[7,9,10,38,41,76] In our experience, a brief duration of symptoms and mild neurologic deficits are associated with a good outcome. Long-standing neurologic disability and traumatic spinal cord injuries are poor prognostic factors. The best that can be anticipated in such cases is to prevent further deterioration and perhaps slightly improve gait and hand function.

For patients with spondylosis who have acute spinal contusion from neck hyperextension,[44] emergency medical treatment consists of administering methylprednisolone sodium succinate, 30 mg per kg of body weight in a bolus, followed by 5.4 mg per kg per hour for 23 hours, to be started within eight hours of injury. In a recent study, patients treated with steroids were neurologically improved at six months' follow-up compared with patients treated with placebo.[77] If indicated, surgical intervention is ideally deferred until spinal cord swelling has resolved and the neurologic state has become stable.

Surgical therapy for spondylotic myelopathy may be through either an anterior or a posterior approach; several large series have failed to establish the superiority of either procedure (Figure 4).[49,76,78-80] Myelopathy caused by osteophytes confined to one or two levels is treated by an anterior operation with the removal of osteophytes.[38,41,51,81,82] In severe cases, radical anterior surgical decompressions are done using multiple-level vertebrectomies and reconstruction with instrumentation.[19] Indications for posterior decompression (that is, laminectomy) are encountered less frequently and include cord compression from posterior structures (that is, ligamentum flavum and hypertrophied facet or laminar bone) and the presence of a developmentally narrow spinal canal (see Figure 2). The treatment of multilevel disease is controversial. Many surgeons prefer laminectomy for multilevel disease,[76,78,83-85] whereas we prefer to treat these patients with an anterior approach. Laminectomy may re-

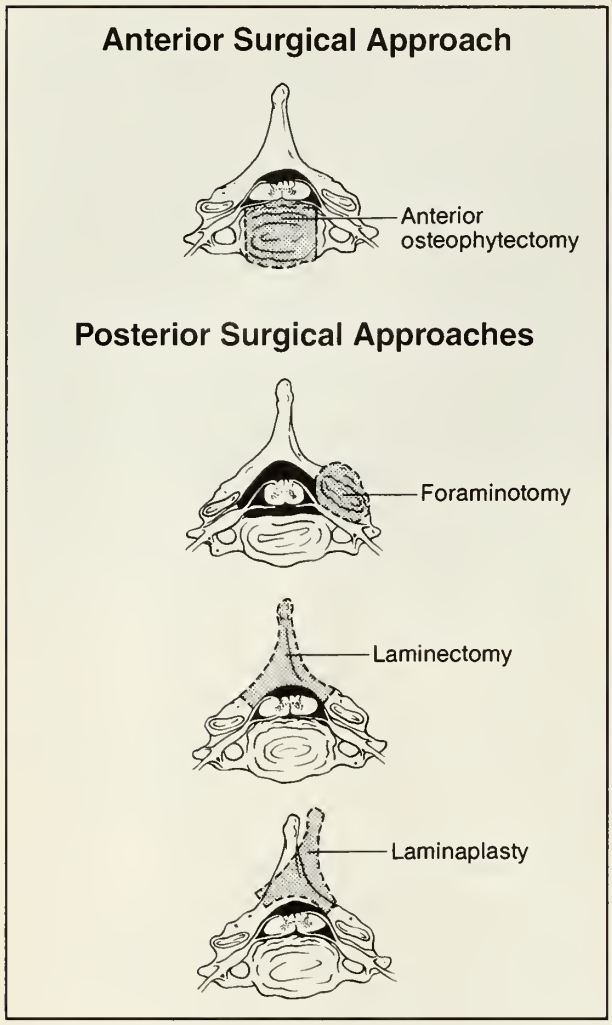

Figure 4.—The anterior and posterior approaches to the cervical cord and nerve roots are depicted. Three posterior procedures are illustrated: laminectomy, foraminotomy, and laminaplasty. Laminaplasty procedures expand the spinal canal by partially removing the lamina and elevating the remaining bone fragments.

sult in spinal instability in as much as 10% of patients and is contraindicated if there is cervical spine kyphosis.[85,86] Laminaplasty, a technique to enlarge the spinal canal by preserving and elevating the lamina roof over the dura, may to some extent prevent spinal instability.[49,87-89]

Recent surgical series using both anterior and posterior approaches show excellent or good results in about 70% of patients with myelopathy.[37,38,49,90-95] Fewer studies report less encouraging results.[41,47,62] In general, results are better with an anterior operation, with improvement reported in 70% to 80% of patients.[49,95-100] Even more impressive results have been reported with radical anterior decompressions (vertebrectomy).[19,81,101-105] The results of an anterior procedure may, in part, be biased favorably because usually the extent of the disease has been limited to one or two levels and follow-up has been short.[76] Misdiagnosis, surgical trauma, inadequate decompression, and irreversible spinal cord injury are important identifiable reasons for a poor surgical outcome.[106-109] At long-term follow-up, functional outcome noticeably declines, but the decline is clearly more pronounced in those patients with a posterior operation.[38,76,91,94,109,110] Delayed neurologic deterioration may occur from disease progression at other levels and spinal instability.[109] About 20% of patients deteriorate without radiologic explanation,[76,106,107] indicating that the pathophysiology of cervical spondylotic myelopathy is still enigmatic.

Cervical Radiculopathy

Radicular symptoms resolve in the majority of patients with simple remedies[34] or without any treatment whatsoever.[39] Treatments include activity modification, neck immobilization, intermittent cervical traction, and isometric exercises when acute neck pain resolves. Nonsteroidal anti-inflammatory agents will usually provide adequate pain relief. Diazepam and narcotics are used sparingly. A short course of steroids—prednisone, 60 mg daily for 7 days and then 5 days tapered—is given occasionally for severe cases. The instillation of steroids into the cervical epidural space may be of benefit in patients with pain that does not resolve with the above therapy.[34]

The indications for surgical intervention are unremitting pain and progressive weakness despite a full trial of nonsurgical management. Anterior and posterior approaches have been used to perform root decompression, with equal results.[33,111] Foraminotomy, or a posterior approach, is preferred for nerve root compression due to facet joint hypertrophy and may be preferred for posterolateral disc herniations. The anterior approach is more appropriate if root compression occurs from osteophyte or disc located anterior to the root (see Figure 4). If an anterior operation is elected, the removal of disc and osteophyte is usually followed by the placement of an interbody strut graft harvested from the hip or from a bone bank. Others prefer not to use a strut graft and claim that perioperative morbidity is reduced, complications of grafting are avoided, and overall clinical results are comparable.[40,112-116] We think that grafting maintains spinal anatomic alignment and neural foraminal patency and maximizes the chance for solid bony fusion. Without a graft, collapse at the discectomy site can cause prolonged postoperative neck pain and narrow the neural foramen at that level, with the potential for the development of a radiculopathy. Instrumentation improves bony fusion rates, but because instrumentation may result in complications, it is generally not warranted in routine cases.

Excellent or good results have been reported in 70% to 80% of patients after surgical treatment of spondylotic radiculopathy using either anterior or posterior approaches.[38,40,42,83] In one study, one or more symptoms recurred in 60% of patients within one to six years after the operation, but episodes of deterioration responded to conservative therapy and rarely required further surgical intervention.[40]

Neck Pain

Neck pain from spondylosis, in the absence of radicular symptoms, will usually respond to conservative therapy as outlined for patients with radiculopathy. Depressed

persons, those using disability for secondary gain, and patients with myofascial pain disorders should be identified. Surgical treatment is not advocated for neck pain from spondylosis.[33] In our experience in treating patients with radiculopathy, localized neck pain from single-level disc disease may resolve with surgical treatment, but pain from multilevel disease responds less predictably.

Summary

Neck pain from cervical spondylosis will usually respond to simple remedies, including activity modification, neck immobilization, isometric exercises, and drugs. For patients with neurologic symptoms, MR imaging is the preferred initial diagnostic study, although CT myelography may still be preferred for evaluating radiculopathy. In most cases of spondylotic radiculopathy, symptoms resolve with conservative therapy, and surgical intervention is not considered unless pain persists or there is progressive neurologic deficit. When indicated, surgical therapy is performed through either the anterior or posterior cervical spine, depending on the site of neural impingement. Surgical results are gratifying, with improvement in 70% to 80% of patients. Myelopathy is the most severe and disabling feature of this disease. The natural history of spondylotic myelopathy is variable, with some patients having nonprogressive minor impairment and others relentless neurologic deterioration. Because the clinical course in any new patient is unpredictable, it is reasonable to treat patients who have minor symptoms with a collar and observe them over time. A third to half of patients improve with this simple remedy. An operation is advocated for moderate or severe disability. In general, anterior cervical approaches are preferred, although there are still indications for laminectomy. Results are modest, with initial satisfactory results expected in 70% of patients. Functional outcome declines with long-term follow-up, but the decline is clearly more pronounced in those patients with a posterior operation. This finding raises the question of whether, and how much, surgical treatment affects the natural course of the disease. Prospective randomized studies will answer these questions.

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Epitomes

Important Advances in Clinical Medicine

Radiology

James M. Halls, MD, and David Larson, MD, Section Editors

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in radiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Radiology of the California Medical Association, and the summaries were prepared under the direction of James M. Halls, MD, David Larson, MD, and the panel.

Percutaneous Core Biopsy of the Breast

CURRENT OPTIONS FOR the tissue diagnosis of nonpalpable breast lesions detected by mammography are needle localization with surgical excision, percutaneous fine-needle aspiration (FNA), and percutaneous core biopsy (PCB). Needle placement for all three methods may be guided by mammography using stereotactic techniques or by ultrasonography using direct visualization. Percutaneous core biopsy has recently emerged as the technique of choice for many patients.

Core biopsy tissue specimens are obtained by using a specially designed 14-gauge biopsy needle matched with an automated biopsy gun. When the gun is fired, a set of springs drives an inner needle forward 23 mm, exposing a 17-mm tissue slot at the tip. A second set of springs immediately drives an outer cutting needle over the tissue slot, trapping a core of breast tissue in the inner needle. In most instances, five core tissue specimens are obtained for histologic diagnosis.

Most centers use dedicated stereotactic mammography equipment with a specifically designed table to guide needle placement for PCB. The patient lies prone with her breast suspended through a hole in the table and compressed by the mammography unit beneath the table. The x-ray tube is moved 15 degrees to both right and left to obtain stereotactic views. Digital mammography devices display images electronically within a few seconds rather than the several minutes required for film. A computer that uses the principles of triangulation calculates the location and depth of the target lesion identified by the operator. A radiologist positions the needle using the computer-generated coordinates. Visualization is adequate for biopsy of most breast masses and microcalcifications. The core specimen is radiographed to confirm the removal of microcalcifications. Ultrasonography may be used to guide the biopsy of any mass that can be visualized sonographically. Most microcalcifications are not identified by ultrasound, however, so sonographic guidance cannot be used for a biopsy.

The advantages of PCB include highly accurate tissue diagnosis, the provision of enough tissue to allow the diagnosis of invasive carcinoma in most cases as well as to do estrogen-receptor analysis and flow cytometry, cost lower than surgical biopsy, and superior patient acceptance. Several series involving a combined total of 1,899 biopsies reported the agreement of the results of PCB with those of surgical biopsies in 90% to 99% of cases when a 14-gauge needle was used and at least five core specimens were obtained. Whereas FNA is limited to cytologic diagnosis and cannot be used to differentiate invasive from noninvasive carcinoma, core biopsy accurately predicts the presence of invasion in 98% of cases and the absence of invasion in 80% of cases. Estrogen- and progesterone-receptor data and flow cytometry studies, performed on core specimens but not possible with FNA, are used to direct patient treatment without surgical biopsy. Inadequate tissue specimens are rare (<1%) compared with the 20% inadequate specimen rate reported for FNA. Direct savings in the cost of PCB compared with surgical biopsy have been calculated at $893 to $2,000 per case. This cost savings is particularly important considering that only about 25% of biopsies of lesions detected by mammography are malignant.

Patient acceptance is high because PCB is performed as an outpatient procedure under local anesthesia, removes a minimum of breast tissue, and leaves little or no discernible deformity or scar. Complications are rare (less than 0.2%) and consist of hematoma and infection, with one reported case of tumor seeding of the needle track. Minor bruising around the biopsy site is common but self-limited. The prone biopsy position virtually eliminates the vasovagal reactions that are common with FNA and needle localizations done in the upright position.

The limitations of PCB include the expense and the limited availability of stereotactic core biopsy mammog-

raphy units, the inability to target some lesions, and the inability of some patients to tolerate the prone position. Centers must have a sufficient volume of biopsies to justify the expense of a single-purpose stereotactic unit, so access to this technique is not yet universally available, although mobile units are in use.

Lesions near the chest wall or in the subareolar cone of breast tissue may be difficult to target. If a patient's breast compresses to less than 2 cm, the 23-mm excursion of the needle must start outside the breast. Ultrasonographic guidance is an effective alternative guidance method in these cases, provided that the lesion can be visualized. Candidates for PCB are patients with a mammographically detected lesion judged to be at high suspicion (70% risk) or moderate to low suspicion (10% to 20% risk) of breast carcinoma. Lesions assessed to be probably benign (less than 2% risk) are best observed mammographically, unless patient anxiety is high.

WILLIAM BRANT, MD
Sacramento, California

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Parker SH, Burbank F, Jackman RJ, et al: Percutaneous large-core breast biopsy: A multi-institutional study. Radiology 1994; 193:359-364

Current Status of Thrombolysis

ARTERIAL THROMBOEMBOLISM is a well-recognized cause of major morbidity and sometimes death. Until recently, the only treatment was surgical: amputation, vascular reconstruction, vascular bypass grafting, and Fogarty balloon embolectomy. With the development of thrombolytic pharmacologic agents, a less invasive method has become available. The first widely used agent, streptokinase, although inexpensive, was prone to hemorrhagic complication, was antigenic with frequent reactions, and could not be administered repeatedly at short intervals. More recently developed agents include tissue plasminogen activator and urokinase. The use of urokinase is associated with few hemorrhagic complications, it is not antigenic, and it is therefore generally accepted as the current agent of choice.

Efficacy has notably improved, and indications have been expanded for thrombolysis. In one method, instead of intravenous administration or simply leaving a catheter dripping urokinase at the leading edge of a thrombosed vessel, a specially designed catheter with many tiny side holes is advanced through a thrombosed segment of vessel. With the end hole occluded by a guide wire, rapid pulses of concentrated urokinase (25,000 units per ml) are delivered with a 1-ml tuberculin syringe. This creates a high-pressure spray through the tiny side slits, directly delivering thrombolytic agent deeply into the clot while macerating it. This advance has led to a pronounced improvement in technical success, fewer hemorrhagic complications, and greatly shortened thrombolytic times. Procedures can now be measured in minutes to hours rather than hours to days.

Another important advance has been the addition of heparin to the urokinase mixture to impede concurrent rethrombosis. A major advantage to this radiologic approach is that frequently an underlying lesion (that is, stenosis) will be uncovered that predisposes the vessel or bypass graft to thrombose. At the same setting, this stenosis can be definitively treated by balloon angioplasty or stenting with generally excellent results.

Modern thrombolysis techniques have also been a boon for hemodialysis patients. It has enabled vascular access sites to be preserved as long as possible, which is critically important for these patients.

In summary, interventional radiologist–directed thrombolysis should now be considered as a first line of therapy in patients with the following disorders: acute thrombosis of peripheral arteries and bypass grafts, including cases of acute critical ischemia; acute embolism of peripheral arteries or bypass grafts; subacute or chronic arterial or graft thrombosis; thrombosed hemodialysis access grafts; venous thrombosis involving veins proximal to dialysis grafts, thoracic outlet syndromes, or portal veins or stents after transjugular intrahepatic portosystemic shunting procedures.

In experienced hands, a technical success rate of about 95% can be expected. The complication rate is about 8%, most of which are groin hematomas or distal emboli requiring minimal management. Life-threatening complications are rare but include intracranial or gastrointestinal bleeding. Close monitoring of clotting factors is therefore required. Exciting new applications now undergoing clinical trials include emergency thrombolytic therapy for pulmonary embolus and acute thromboembolic cerebrovascular stroke.

JAMES J. SELL, MD
FREDERICK W. RUPP, MD
ROBERT J. TELEPAK, MD
Albuquerque, New Mexico

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Magnetic Resonance Imaging, Positron Emission Tomography, and Single-Photon-Emission Computed Tomography in Epilepsy

RECENT TECHNOLOGIC ADVANCES in imaging have launched us into an era of improved diagnosis and localization of the pathologic substrate of epilepsy, the epileptogenic zone. Published articles cannot substantiate the use of a solitary modality in investigating a patient with seizures. Because magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon-emission computed tomography (SPECT) measure

different aspects of brain function and anatomy, including structure, metabolism, and blood flow, respectively, the three modalities are complementary; each makes a unique contribution to the investigation of patients' seizures.

Magnetic resonance imaging exceeds PET and SPECT imaging in its ability to show structural abnormalities. Reported sensitivity and specificity vary. In studies that report the surgical success of seizure control, sensitivities for diagnosis by MRI vary from 80% to 90% for sclerosis due to trauma, infection, or infarction; 90% to 95% for mesial-temporal sclerosis; 90% to 100% for neuronal migration disorder; and 100% for tumor or vascular malformation. High-resolution imaging with three-dimensional volume techniques and 1.5-mm contiguous slices has led to a better detection of cortical dysplasias, hamartomas, and other developmental abnormalities. Three-dimensional data are not necessarily viewed in three-dimensional format, but it allows reformatting of the images in any plane to facilitate distinguishing subtle gyral or cortical abnormalities from normal configurations and to compensate for malalignment of the patient.

For difficult cases in which the electroencephalographic data localize the seizures, but the MRI scan is normal, surface rendering of three-dimensional volume data obtained with MRI has helped radiologists to detect previously occult structural abnormalities. Mesial-temporal sclerosis, the most common cause of temporal lobe epilepsy, is characterized by cell loss and astrogliosis that involves a small portion of the hippocampus. Before advances in spatial resolution, early studies reported MRI to be poorly sensitive to the changes of mesial-temporal sclerosis. The demonstration of atrophy and increased signal in a temporal lobe with high-resolution MRI scans now has a high correlation with successful postsurgical seizure control. Volumetric analysis of MRI images has further improved the sensitivity of MRI in the diagnosis of mesial-temporal sclerosis. Side-to-side differences detected with magnetic resonance–based hippocampal volumetry correlates with cell loss quantified at histology. When electroencephalographic evidence of the start of a unilateral temporal lobe seizure is concordant with predominantly unilateral temporal lobe atrophy by MRI volumetric analysis, there is a greater than 90% chance of an excellent surgical outcome compared with 50% surgical success when volumetric evidence for unilateral atrophy is absent on MRI. The identification of a lesion on MRI in extratemporal areas also correlates with successful postsurgical seizure control.

Functional MRI uses ultrafast scanning techniques to scan patients while they are doing a task that is known to activate specific cortical regions, for example, the sensorimotor cortex. The technique is used to define the relationship of an epileptogenic pathologic substrate (such as tumor) to functionally eloquent cortex before surgical resection and thereby to avoid unacceptable postsurgical deficits.

The structural abnormalities seen with MRI correlate highly with the epileptogenic zone, but are not definitive. Therefore, MRI cannot be used alone. The epileptogenic zone is highly likely to be within a zone of altered metabolism or blood flow as seen with PET and SPECT, respectively. Both modalities have a relatively high sensitivity—PET, 70% to 80% for interictal scans; SPECT, 73% and 97% for peri-ictal and ictal scans, respectively—and moderate specificity for the diagnosis of temporal lobe epilepsy. Lower sensitivities are seen in patients with extratemporal seizures. Although metabolism and blood flow increase during ictal events and decrease interictally, the detection of metabolic changes by PET with the use of fludeoxyglucose F 18 is known to be more sensitive. Although the spatial resolution for modern clinical PET scanners is typically 5 to 7 mm, the added advantages of wider availability, reduced cost, and greater feasibility of ictal scanning with SPECT after administering hexamethyl-propyleneamine oxime (HMPAO) make this modality the more practical tool. Typical resolution for a modern three-head SPECT camera is 6 to 8 mm. Truly ictal studies are possible with HMPAO-SPECT studies because there is rapid uptake of the radiotracer but little washout, so the functional image represents activity during the time of administration and remains bound to the brain for several hours, which facilitates administering the radiotracer at ictus and scanning as long as four hours later. Seizure localization is most reliable when the radiotracer is administered early at the start of seizures and when a seizure does not propagate or does so minimally.

BRIAN W. CHONG, MD
DAVID K. SHELTON, MD
Sacramento, California

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Imaging of Appendicitis

Most patients with acute appendicitis have classic clinical findings and are treated surgically. About a third of patients have atypical or confusing clinical findings and often require radiologic imaging. Abdominal radiographs and barium enema have been used in the past to aid in the diagnosis of acute appendicitis. Recently, the use of real-time ultrasonography and computed tomography (CT) has been advocated in patients with this possible diagnosis. The ultrasound examination involves graded compression in the right lower quadrant and especially in the area of maximal tenderness. Because of advances in technology and familiarization with expected sonographic findings, a normal appendix is frequently visualized, excluding the diagnosis of appendicitis. Diagnostic criteria for acute appendicitis in both children and adults include a distended appendix that is greater than 6 mm in diameter, lacks compressibility and peristalsis, and is constant in shape. Findings that are strongly suggestive include pericecal inflammation or abscess. Visualization

of an appendicolith increases the specificity. In cases of appendiceal perforation, the appendix itself may be difficult, if not impossible, to visualize. A pericecal loculated fluid collection suggests perforation, whereas free intraperitoneal fluid is not a predictor of perforation.

With color Doppler ultrasonography, increased blood flow can be seen in areas of inflammation. Although this technique can increase observer confidence, it does not increase the sensitivity in detecting acute appendicitis. Recent studies have shown the use of sonography for the diagnosis of appendicitis to have a sensitivity of 76% to 100%, a specificity of 89% to 97%, and an accuracy of 83% to 97%. The ultrasound diagnosis of appendicitis is somewhat limited by the presence of obesity, ascites, and severe abdominal pain and can be more difficult if an appendix is retrocecal. Ultrasonography, however, is useful in evaluating the abdomen and pelvis for other disease if scanning of the right lower quadrant is not diagnostic for appendicitis. In children, other possible disorders that can be revealed with ultrasonography include mesenteric adenitis, ileitis, intussusception, Crohn's disease, Burkitt's lymphoma, foreign body, and neutropenic colitis.

Computed tomography has also been used to evaluate atypical clinical findings of appendicitis and can be highly specific even without the use of intravenous or oral contrast media. Computed tomographic criteria include the visualization of an abnormal appendix with fat stranding in the pericecal area or an appendicolith with a right lower quadrant abscess or phlegmon. The sensitivity, specificity, and accuracy for the CT diagnosis of acute appendicitis range from 87% to 98%, 83% to 97%, and 83% to 97%, respectively. Computed tomography can be used to detect complications of appendicitis such as hepatic abscess, small bowel obstruction, and mesenteric venous thrombosis and to evaluate concurrent disorders. It is also useful in the guidance of percutaneous appendiceal abscess drainage procedures.

Although there is a small false-negative and false-positive rate for the diagnosis of appendicitis using either ultrasonography or CT, both modalities can be extremely useful. Ultrasonography may be most beneficial in children and young women because of the lack of ionizing irradiation, lower cost, and positive predictive value. Equipment is portable if necessary. In women of childbearing age, graded compression ultrasonography in conjunction with an endovaginal ultrasonogram is useful for evaluating acute gynecologic disorders. Computed tomography is advantageous in that it is tolerated by sick patients, is not operator-dependent, and the results are not affected by the amount of bowel gas or abdominal pain.

REBECCA HULETT, MD
Tucson, Arizona

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Spiral and Ultrafast Computed Tomography for Noninvasive Cardiac Imaging in Children

CONGENITAL HEART DISEASE is a serious health problem in the United States, affecting about 8 of 1,000 newborns. With the recent dramatic improvements in postoperative survival of infants with even the most serious and complex congenital cardiac malformations, emphasis has been placed on improving cardiac function, neurologic outcome, and the quality of life. Imaging studies play an important role in the management of these patients.

During the past decade, the need for cardiac catheterization with projectional angiocardiography has decreased with the use of less invasive cross-sectional imaging techniques such as echocardiography and magnetic resonance imaging. Computed tomography (CT) combines high spatial and contrast resolution with tomographic imaging, eliminating the superimposition of complex cardiac anatomy and surrounding lung and bony chest wall. The recent development of spiral and ultrafast (electron beam) CT techniques has extended its application to cardiovascular imaging (CT angiocardiography) with less motion artifact due to heartbeat and respirations. In adult abdominal and peripheral vascular disease, CT angiography has yielded results comparable to those of projectional angiography, with less radiation exposure, reduced requirements for contrast material, and no need for invasive catheterization of the vascular system. In the chest, CT angiography is most useful in the diagnosis of pulmonary embolism and in congenital heart disease, where there is a need for exactly delineating complex cardiovascular anatomy.

In infants and children, because of their small size, the entire thorax can be covered with spiral CT in 20 to 30 seconds during peak contrast enhancement given through a peripheral vein. Motion is further reduced by having older cooperative children hold their breath during the scan. Young children can be scanned successfully during quiet respiration, and sedation is less frequently needed because of the rapid acquisition time of the CT data. Imaging data are initially reconstructed as axial slices, familiar from conventional CT. Because the data are collected from a large volume of tissue rather than a slice at a time, they can be subsequently reconstructed and viewed on a computer work station from different angles in user-selected cross-sectional planes and three-dimensional renditions best suited to display complex cardiovascular relationships, without the need to administer additional contrast media.

Respiratory and cardiac motion can be further suppressed by means of ultrafast (electron beam) scanning. Slice acquisition time is about 100 milliseconds, and, when using the dynamic imaging mode, the images are virtually motion-free even in dyspneic or crying children. Multislice bolus tracking (flow) techniques can be used to visualize hemodynamic events in real time and to calculate shunt fractions. Cardiac gating is used to link image acquisition to events in the cardiac cycle, allowing the reconstruction of multislice cine sequences, which are used to evaluate regional ventricular wall motion and to calculate

functional indices—systolic and diastolic ventricular volumes, cardiac output, and ejection fraction.

Computed tomographic angiocardiography provides valuable anatomic information in three dimensions regarding the size and structure of cardiac chambers, the caliber of pulmonary arteries and aorta, septal defects, the connection between ventricles and great vessels, the compression of airways by vascular structures, and position and patency of shunts and stents. In most cases, the image information is analogous or even superior to that provided by conventional projectional angiocardiography. Computed tomography uses less contrast material and radiation dose than angiography, which often requires administering multiple doses and biplane filming in various projections.

Although cardiac catheterization is still required for percutaneous interventions—balloon dilatation, stent placement, and embolization—and it is the only test to measure intracardiac and intravascular pressure curves and oxygen saturation, electron-beam CT can also provide detailed functional information, as mentioned earlier.

Emerging indications for cardiac CT are as follows: possible aortic coarctation; preoperative evaluation of pulmonary vascularity in patients with cyanotic heart disease who are being considered for palliative shunt placement; unifocalization of aortopulmonary collaterals or complete repair; assessment of complex postoperative anatomy; and the visualization of airway compression by vascular rings, slings, dilated vessels, and shunts. If cardiac catheterization is still required to further assess cardiac function and to guide endovascular intervention, the performance of cardiac CT on the day before catheterization substantially reduces the number of administrations and projections, the amount of contrast material required, and the procedure time, which should lead to savings in radiation dose and costs. Close cooperation between radiologists and pediatric cardiologists is required, especially in the user-interactive three-dimensional rendering and interpretation of the CT data. Noninvasive high-resolution "four-dimensional" cardiac imaging with CT has now become a reality, and its more general application in multidisciplinary cardiovascular research and treatment centers should have an important influence on patient management and outcome.

SJIRK J. WESTRA, MD
Los Angeles, California

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Doppler Ultrasonography of Transjugular Intrahepatic Portosystemic Shunts

THE TRANSJUGULAR INTRAHEPATIC portosystemic shunt (TIPS) procedure is a nonoperative treatment option for managing variceal hemorrhage from portal hypertension. In this percutaneous procedure, an expandable metallic stent is placed in the liver to create a channel between a hepatic vein and a portal vein. Its creation has been shown to be feasible and effective, and it has become an accepted method for treating patients with portal hypertension and acute variceal bleeding. These shunts can become stenotic or occluded, however. Because the likelihood of shunt complications increases with length of time since insertion and the risk of recurrent variceal bleeding is directly related to shunt patency, a noninvasive, widely available, and relatively inexpensive means for assessing shunt function is of great importance.

Sonography is a valuable diagnostic tool in the noninvasive evaluation of hepatic parenchymal disease and hepatic vasculature. With the use of Doppler sonography, functional hemodynamic information regarding vascular patency, flow direction, and flow patterns can be obtained. Doppler sonography has been used to evaluate conventional, surgically created portosystemic shunts, and recent reports have shown this technique to be of value in demonstrating changes in hepatic hemodynamics after TIPS placement. The intrahepatic location of the TIPS makes it amenable to sonographic assessment. On gray-scale sonographic imaging, the walls of the stent are seen as highly echogenic parallel lines. Sonographic protocol includes spectral and color Doppler insonation of the main and intraparenchymal right and left portal veins, the TIPS stent, and the hepatic veins. The shunt is imaged along its long axis, and the maximum flow velocity within the TIPS is measured. The peak flow velocity by Doppler ultrasonography within a patent TIPS ranges from 50 to 270 cm per second.

Doppler sonography demonstrates TIPS flow and detects thrombosis. The absence of detectable flow within a TIPS indicates shunt thrombosis. Several Doppler sonographic variables have been studied in an effort to investigate which changes are most indicative of shunt dysfunction and, in particular, of TIPS stenosis. The variables that have been used include portal vein flow velocity and portal blood flow, maximum flow velocity within the shunt, the direction of flow within the intrahepatic portal venous branches, temporal change in peak stent velocity, and the direction of flow in the draining hepatic vein.

Reduced maximum flow velocities within a TIPS, measured in the intrahepatic portion of the stent, suggest stenoses that most often occur downstream, at the hepatic venous end of the shunt, or in the draining hepatic vein. Doppler measurement of a maximum flow velocity within the TIPS of 50 cm per second or less is a useful and suggestive indication of shunt stenosis.

Routinely doing baseline postprocedure and follow-up Doppler sonographic studies in patients with TIPS aids in screening for shunt complications and in selecting patients who will benefit from therapeutic intervention, including revising stenotic shunts. Although long-term complications are known to occur, TIPS function can be

maintained in most patients by careful surveillance and periodic percutaneous angiographic intervention when indicated. The long-term clinical effect of routine screening by Doppler ultrasonography is not yet known, but the early detection and prompt revision of occluded or tightly stenotic shunts will likely decrease the frequency of recurrent variceal bleeding.

VICKIE A. FELDSTEIN, MD
MAITRAY D. PATEL, MD
San Francisco, California

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Spiral Computed Tomography and Magnetic Resonance Imaging in the Detection of Pulmonary Emboli

PULMONARY EMBOLISM following lower extremity deep venous thrombosis is the third most common cardiovascular disease. The initial assessment of pulmonary embolism begins with a high index of suspicion. This is difficult because pulmonary emboli often present with nonspecific chest radiographs and normal arterial gas measurements and electrocardiograms. The current imaging workup of pulmonary embolism includes varying combinations of peripheral venous ultrasonography, ventilation-perfusion scanning, and pulmonary angiography.

Ventilation-perfusion scanning is perhaps the best known tool to aid in the diagnosis of pulmonary embolism. This is only an indirect test for pulmonary embolism that uses multiple scintigraphic criteria to arrive at a probability or likelihood for pulmonary embolism, rather than direct visualization. A normal scan virtually excludes the diagnosis whereas a low-probability scan, combined with a low pretest probability, lowers the likelihood of pulmonary embolus enough to preclude the use of angiography or anticoagulation in most patients. When a high-probability scan is coupled with a high pretest probability, the likelihood of pulmonary embolism being present exceeds 95%.

Unfortunately, most patients do not fall into these diagnostic categories, where pulmonary embolus can be reliably confirmed or excluded. (This remains true despite the recent revision of the Prospective Investigation of Pulmonary Embolism Diagnosis [PIOPED] criterion that broadens the definition of a low-probability scan.) This unreliability of ventilation-perfusion scanning in most clinical situations, combined with the perceived cost and morbidity of pulmonary angiography, has helped spur the recent interest in the development and application of new imaging techniques.

Spiral computed tomography (CT), which is becoming widely available, can now directly visualize pulmonary emboli noninvasively. Conventional CT requires relatively long scan times that, combined with respiratory motion, create artifacts that severely limit its usefulness as a screening tool for pulmonary embolism. Spiral or helical CT acquires images as a volume (cylinder) of data rather than a slice at a time as with conventional CT scanning. This volume can be acquired in a single breath, thereby diminishing motion artifact. The images are viewed as slices taken from this volume, and if these slices are overlapped, other types of artifact (volume averaging) are diminished.

Spiral CT for pulmonary emboli is done with the administration of 100 to 150 ml of a contrast medium intravenously through a power injector. It is given at 3 to 4 ml per second, which requires good peripheral venous access. During the contrast infusion, the scanner acquires one or two volumes of data, which requires either a 12- to 15-second or a 24- to 30-second breath hold, respectively. Timing of the contrast bolus with respect to the scanning is crucial. To select the best timing for the study, a small bolus of contrast medium may be administered, with preliminary scanning done through the main pulmonary arteries. This step can be particularly helpful in patients with pulmonary hypertension and other cardiac diseases who might have abnormal circulation times.

In many recent comparisons with angiography, spiral CT done in this manner has shown specificity and sensitivity of 90% or more for main, lobar, and segmental pulmonary emboli. The diagnosis of segmental pulmonary emboli, however, requires optimal technique and may necessitate slicing the imaged volume in planes along the axes of pulmonary vessels that run obliquely through the lung. An excellent knowledge of hilar and pulmonary vascular anatomy is also important so that false-positive and false-negative diagnoses are avoided. Hilar nodes, congestive heart failure with perivascular edema, and partial opacification of pulmonary veins can all simulate filling defects and are possible sources of false-positive interpretations.

Because of these problems, spiral CT may fail to detect small emboli. Even with an optimal technique and image reconstructions, the accuracy of spiral CT for the detection of pulmonary emboli beyond the segmental level is less than that of conventional pulmonary angiography. Isolated small emboli are probably rare, however. In the PIOPED trials, a solitary pulmonary embolus distal to a segmental level occurred in only 14 of 251 patients.

Recent technologic advances have also allowed the pulmonary vasculature to be visualized with magnetic resonance imaging (MRI). This is achieved using faster pulse sequences with shorter echo times, body coils, and by timing image acquisition to specific phases in the cardiac and respiratory cycle (cardiac and respiratory gating). The advantage of MRI in the evaluation of thromboembolic disease is twofold. First, it can provide three-dimensional images of the pulmonary vascular bed in multiple projections without requiring the administra-

tion of iodinated contrast materials. Concurrent peripheral MRI venography can also be done to evaluate for the presence of deep venous thrombi. The ability to evaluate for both pulmonary embolism and deep venous thrombosis in less than an hour makes MRI an attractive modality in the diagnosis of thromboembolic disease.

Unfortunately, the hardware and software necessary to produce clinically useful images of the pulmonary vascular tree are not yet widely available or widely used. Spiral CT is more widely available and can better evaluate the lung parenchyma and mediastinum as well as the pulmonary vasculature. Therefore, it can detect other disease processes that could mimic pulmonary embolism on ventilation-perfusion scans.

MARK BALDECK, DDS, MD
LOREN KETAI, MD
Albuquerque, New Mexico

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Magnetic Resonance Imaging of Radiographically Occult Bony Trauma

SUBSTANTIAL BONY INJURIES related to acute trauma or repetitive stress may not be detected on plain radiographs. Magnetic resonance imaging (MRI) has proved to be a powerful tool to assess these radiographically occult injuries, primarily because of its ability to show associated changes in the underlying marrow.

Trabecular bone is commonly injured during athletic activities. "Bone bruises" may be the sole cause for a patient's symptoms, and occasionally may result in adverse long-term sequalae if not treated appropriately. Plain radiographs are notoriously insensitive for detecting trabecular injuries because the overlying cortex is often intact. Because of its exquisite soft tissue contrast, MRI is able to depict the associated marrow hemorrhage or edema. Its ability to display concomitant soft tissue injuries is one advantage of this technique compared with radionuclide bone scanning.

Nondisplaced fractures may also be missed on plain films. Occult hip fractures in elderly patients present a particular diagnostic challenge because a radionuclide bone scan may be normal for the first few days after injury in these patients. Again, because of its sensitivity for detecting associated marrow changes, MRI can rapidly detect occult fractures with a high degree of accuracy. Similarly, a normal MRI virtually excludes serious bony injury, thereby allowing efficient patient evaluation. If a limited protocol is used, this technique can be cost-competitive with other modalities such as a radionuclide bone scan, often with greater specificity.

Stress fractures are becoming more common in our increasingly active society. Rapid, accurate diagnosis is important because clinical assessment can be difficult, and biopsy in the early stages of stress injury may result in a mistaken diagnosis of neoplasm due to the presence of immature cells related to the reparative process. Plain radiographs are insensitive in these early stages, but MRI is able to detect the associated marrow changes and sometimes a distinct fracture line as well, before the typical periosteal reaction or fracture is detectable on plain films. As such, it is a useful diagnostic adjunct when a radionuclide bone scan is indeterminate.

Although the use of MRI has come under scrutiny because of current economic forces, it may prove to be the most cost-effective means for arriving at a rapid and accurate diagnosis in a patient with a radiographically occult bony injury.

MARK ANDERSON, MD
Davis, California

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Magnetic Resonance Imaging of the Breast

MAGNETIC RESONANCE (MR) mammography has been under technical and clinical evaluation for more than 14 years. Although initial data clearly indicate the suitability of MR imaging of the female breast, the use of MR mammography in evaluating breast disease has yet to be fully realized. Current applications are limited to the diagnosis of cancer in selected patients, the staging of known breast cancer, and the evaluation of silicone implant integrity.

Magnetic resonance mammography has undergone extensive evaluation as a noninvasive means for distinguishing between benign and malignant breast lesions identified by conventional mammography. Among the currently available imaging modalities—mammography, sonography, thermography, and computed tomography (CT)—only the use of mammography has been able to show a substantial reduction in the mortality associated with breast cancer, particularly for women older than 50 years. By using repetitive MR imaging of the same slices before and at short intervals after the administration of a contrast medium, known as "dynamic MR mammography," an 88% to 100% sensitivity in differentiating benign from malignant lesions has been reported. In the absence of contrast enhancement, a carcinoma can be excluded with a high degree of certainty.

The greatest enthusiasm for MR mammography in evaluating breast disease is as a screening tool for the large number of women with mammographically dense breasts and a relatively increased risk for breast cancer due to a strong family history of the disease.

Mammographically dense breasts make the exclusion of small tumors difficult. This is particularly worrisome in high-risk patients. The characteristic changes of dynamic MR mammography are capable of discriminating these lesions. Moreover, the characteristic changes are known to apply only to active tumor regions and not to necrotic or fibrotic regions.

Magnetic resonance imaging of the breast in patients with silicone prostheses has proved to be highly accurate in identifying the common complications associated with the implants and in characterizing concurrent disease. A silicone breast implant has a uniform signal intensity that is easily distinguished from pectoralis muscle and breast parenchyma. This permits obvious positioning of the breast implant in relation to adjacent anatomic structures. Ruptured and intact implants are immediately differentiated with a high degree of specificity using MR mammography. Moreover, when implants are found to be ruptured, MR mammography is able to demonstrate whether the silicone material remains within the fibrous surgical capsule or has extravasated into surrounding tissue. In patients with trauma, MR mammography can distinguish a hematoma in the breast parenchyma from silicone that has extravasated into the surrounding tissues.

Although there is a need to identify in which women there is a high risk of breast cancer developing, the widespread use of MR mammography as a screening tool for the disease is not economically feasible because of its high cost. Cost analysis indicates that MR mammography is useful as a diagnostic adjunct to conventional breast imaging modalities that are difficult to interpret due to mammographically dense breasts, surgical scarring, or the presence of silicone implants.

ROBERT ROSENBERG, MD
LAURENCE D. CAMBRON, PhD, MD
MICHAEL R. WILLIAMSON, MD
Albuquerque, New Mexico

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Radiosurgery

EACH YEAR MORE THAN 100,000 people in the United States are diagnosed with a benign or malignant brain neoplasm. Recent media reports focusing on radiosurgery, a relatively new treatment designed to halt neoplastic growth in the central nervous system, have raised expectations for cure or improved local control over standard treatments. Although not all patients are candidates for radiosurgery, an understanding of its mechanics, indications, selection factors, results, and cost is helpful when responding to patient inquiries or referring patients to radiosurgical facilities.

Radiosurgery, a noninvasive irradiation technique using stereotactic methods, is performed with narrow intersecting beams of one of three types of penetrating radiation: gamma rays produced by the decay of cobalt 60 in a Gamma knife (a specialized apparatus whose sole function is radiosurgery), x-rays produced in standard linear accelerators that have been modified to do radiosurgery, and charged particles such as protons or other ions produced by a cyclotron or synchrotron. No radiosurgical method currently has a clinically demonstrable advantage over another. Although there are a large number of linear accelerators in the United States, most patients are treated on Gamma knife machines. In each case, the intent is to produce cell death or blood vessel thrombosis of targeted tissue within a small, well-defined volume. Accurate targeting is required because the intense radiobiologic effects produced by a single high dose of radiation could result in radionecrosis of normal central nervous system (CNS) tissue. With current technology and commonly used doses, the risk of radionecrosis is often claimed to be less than 5% in many patients, but approaches 20% in patients with malignant gliomas.

The radiosurgical procedure involves a sequence of tasks: temporarily attaching a stereotactic frame to the patient's head, obtaining stereotactic radiologic images of the target and surrounding structures, delineating the target contour on the images, planning treatment by interactively displaying dose contours on computer monitor views of the images, positioning the frame with respect to the radiation beams, and irradiating the target in a single session. The entire process takes a day to do and requires a radiation oncologist, a neurosurgeon, a radiologist, a physicist, and a nurse; in some cases, such as those of children, an anesthesiologist may also be required. Patients are comfortable throughout the procedure, and most return to baseline activity in a day or two.

About 50,000 patients worldwide have been treated with radiosurgery, mostly in the past five years. About a third of these had arteriovenous malformations, a third had benign tumors (such as acoustic neuroma and meningioma), and a third had malignant tumors (glioblastoma, astrocytoma, and metastatic tumors). Clinical reports show that patients selected for treatment should have good neurologic function and a radiologically well-defined target. Most important, the target should be small—usually less than a few centimeters in maximum dimension. For larger targets, it may be impossible to select a dose that provides both a high chance for cure and a low risk for complications. This inverse relationship of dose and volume is supported by clinical experience and radiobiologic theory. Because the target is small, previous irradiation is not a contraindication to radiosurgery.

Numerous retrospective studies have shown that about 35% of arteriovenous malformations selected for radiosurgery are no longer angiographically visible within a year and 85% within two years. Permanent neurologic complications attributable to radiosurgery occur in fewer than 5% of patients treated by experienced teams. These complications may take months or even years to develop, however. Angiographic resolution of the arteriovenous malformation after radiosurgery appears to be equivalent

to that of complete surgical resection; in either case, the risk for hemorrhage is virtually zero. The advantage of radiosurgery is that it is noninvasive and requires minimal hospital stay compared with open surgery. On the other hand, protection from hemorrhage is delayed until the malformation is obliterated by radiosurgery, whereas total resection immediately eliminates the risk for hemorrhage. Many physicians think that small arteriovenous malformations in the brain stem or in other hard-to-reach areas are best treated by radiosurgery. For those located in other areas, the immediate surgical risks must be weighed against the risk of delayed hemorrhage during the latent interval after radiosurgery.

The intent of radiosurgery for benign and malignant tumors is to prevent progression of the radiologic abnormality rather than to cause its complete disappearance—which occasionally occurs, but requires a high radiation dose to achieve consistently. Thus, serial scans—at intervals that depend on the tumor type—following radiosurgery are required. About 90% of acoustic neuromas selected for radiosurgery are controlled (do not progress). In the past five years, recommended radiosurgical doses for acoustic neuromas have been reduced, and the risks of facial and trigeminal neuropathy have been greatly decreased. Retrospective data show, however, that patients with useful hearing on the affected side still have a substantial risk for hearing loss. Whether radiosurgery or traditional surgery is the better therapy for acoustic neuroma is a topic of lively debate, especially because at least transient symptoms may occur after radiosurgery. About 95% of meningiomas selected for radiosurgery are controlled.

The standard treatments of glioblastoma and anaplastic astrocytoma include surgical excision, radiotherapy, and chemotherapy, but recent randomized trial results show a survival benefit for those patients who also receive a brachytherapy boost (temporary implantation of highly active radioactive iodine seeds in removable plastic catheters). Because radiosurgery produces a dose distribution similar to that of brachytherapy, it is now offered at many centers, either initially in conjunction with fractionated radiotherapy or as the only radiation procedure at recurrence. Several retrospective studies show that survival following radiosurgery is similar to that following brachytherapy, but this has not been confirmed in a randomized trial.

Brain metastases are usually well defined and noninfiltrative and therefore represent ideal radiosurgical targets. Retrospective studies show that the growth of targeted tumors is halted for six months in about 90% of cases and that patients then are more likely to die of systemic rather than CNS disease. Therefore, patients with CNS metastasis who derive the greatest benefit from radiosurgery are those who have no or minimal non–CNS metastases. Some studies show that radiosurgery may be useful for some patients with multiple CNS metastases, particularly if their primary disease is controlled and they have no evidence of non–CNS metastases. A current randomized trial should determine whether patients who receive radiosurgery at the time of diagnosis should also receive whole-brain radiotherapy.

Radiosurgery is appealing to patients because it is noninvasive and because the results of treatment compare favorably with those of alternative therapies. Although the typical cost per procedure of radiosurgery is greater than that of radiotherapy, it is less than that of an operation. Studies will help determine whether larger targets can be treated effectively and safely and whether radiosurgery results can be improved with radiosensitizers. In the future, we are likely to see radiosurgery techniques used at non–CNS anatomic sites.

DAVID A. LARSON, PhD, MD
MICHAEL W. McDERMOTT, MD
San Francisco, California

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Alerts, Notices, and Case Reports

Tension Pneumoperitoneum

STEPHANIE Y. CHAN, MD
CARL M. KIRSCH, MD
WILLIAM A. JENSEN, MD
JOHN SHERCK, MD
San Jose, California

PNEUMOPERITONEUM IS a well-known consequence of gastrointestinal perforation, mechanical ventilation, and abdominal operations. Free intraperitoneal gas is usually a marker of underlying disease and does not in itself pose a hazard to a patient. Tension pneumoperitoneum, on the other hand, is a rare complication in which intraperitoneal gas, under pressure, causes hemodynamic and ventilatory compromise, necessitating urgent intervention. We report the case of a mechanically ventilated patient in whom tension pneumoperitoneum developed and describe a simple test that confirmed that the pneumoperitoneum resulted from pulmonary barotrauma.

Report of a Case

The patient, a 60-year-old woman, was admitted to the intensive care unit for hemoptysis and renal failure. She had been healthy until three months before admission, when weakness and anorexia developed, with weight loss. Her hematocrit was 0.25 (25%), and her serum creatinine level was 221 μmol per liter (2.5 mg per dl). An upper gastrointestinal series was normal, and a stool occult blood test was negative. Two weeks before admission, shortness of breath developed, and she had hemoptysis, night sweats, chills, and fever. On admission, her temperature was 38.7°C (101.6°F), her blood pressure was 150/70 mm of mercury, her pulse rate was 108 beats per minute, her respirations were 24 per minute, and oxygen saturation was 94% while the patient was breathing supplemental oxygen at 4 liters per minute by nasal cannula. She was thin, ill-appearing, and in moderate respiratory distress. Her lungs had diffuse rales, there was no cardiac murmur, and her abdomen was unremarkable. Relevant laboratory data included a hematocrit of 0.17 (17%), serum creatinine level of 574.6 μmol per liter (6.5 mg per dl), and a urinalysis that showed erythrocyte casts. An arterial blood gas measurement showed a pH of 7.35, a P_{CO_2} of 35 mm of mercury, and a P_{O_2} of 53 mm of mercury with the patient breathing room air.

Her chest radiograph showed bilateral diffuse alveolar infiltrates with sparing of the left upper lobe (Figure 1).

The combination of pulmonary hemorrhage and glomerulonephritis strongly suggested an autoimmune disease such as Wegener's granulomatosis or antiglomerular basement membrane disease. The patient was started on a regimen of intravenous ceftazidime and clindamycin and treated empirically for autoimmune diseases with daily plasmapheresis and the administration of cyclophosphamide and high doses of methylprednisolone sodium succinate. She was intubated on the third hospital day for respiratory fatigue and progressive oxygen hemoglobin desaturations as low as 80% while receiving supplemental oxygen. A percutaneous needle biopsy of the left kidney showed crescentic glomerulonephritis without vasculitis, but there were no glomeruli available for immunofluorescent staining. On the fourth hospital day, a right tension pneumothorax developed after the patient had bronchoscopy and bronchoalveolar lavage. She was also noted to have a pneumomediastinum and massive subcutaneous emphysema. Insertion of two chest tubes returned the patient's hemodynamic and ventilatory status to baseline.

Figure 1.—The patient's admission chest radiograph shows diffuse alveolar infiltrates.

On the 13th hospital day, while chest tubes and mechanical ventilation were still in use, tense abdominal distention suddenly developed. The patient's blood pressure dropped from 140/60 to 80/50 mm of mercury, her pulse rate increased from 120 to 150 per minute, and her oxygen hemoglobin saturation decreased from 100% to 82% on an inspired oxygen fraction of 80%. The mechanical ventilator was set at a tidal volume of 500 ml, a positive end-expiratory pressure of 5 cm of water, and a pressure support of 10 cm of water in the intermittent mandatory ventilation mode at a rate of 22 per minute. The peak inspiratory pressure increased from 50 to greater than 100

(Chan SY, Kirsch CM, Jensen WA, Sherck J: Tension pneumoperitoneum. West J Med 1996; 165:61-64)

From the Department of Medicine (Drs Chan, Jensen, and Kirsch) and the Department of Surgery (Dr Sherck), Santa Clara Valley Medical Center, San Jose, California.

Reprint requests to Stephanie Y. Chan, MD, Dept of Medicine, Santa Clara Valley Medical Center, 751 S Bascom Ave, San Jose, CA 95128.

Figure 2.—This abdominal radiograph shows tension pneumoperitoneum with massive free intraperitoneal gas causing medial displacement of the liver and elevation of the diaphragm.

cm of water, the abdomen became even more distended, and ventilation was greatly impaired. The patient was removed from the mechanical ventilator, and AmbuBag ventilation was attempted without improvement. An emergency abdominal film revealed a massive amount of intraperitoneal air with medial shifting of the liver and the elevation of both hemidiaphragms (Figure 2). A chest radiograph showed the endotracheal tube and chest tubes in good position, without recurrent pneumothorax. The patient was on nasogastric suction throughout the event, without any improvement. A No. 16-gauge intravenous catheter was inserted percutaneously into the peritoneal cavity in the right upper abdominal quadrant, and an immediate rush of odorless gas was accompanied by pronounced improvement in the patient's hemodynamics and oxygenation. This temporary catheter was then exchanged over a guide wire for a 10F pigtail soft biliary drainage catheter with end and side holes. On two occasions, the abdominal drainage catheter became kinked under the patient, causing her abdomen to become rapidly tense and ventilation to become difficult until catheter patency was restored.

Perforation of the gut as a cause of the tension pneumoperitoneum was deemed unlikely because the patient continued to have normal bowel sounds. Instead, we thought that the gas causing the pneumoperitoneum originated from the thoracic cavity because such rapid, pressurized gas accumulation could be generated by the mechanical ventilator. We therefore sampled gas simultaneously from the chest tubes and the abdominal drain with 30-ml silicone-coated glass syringes and obtained radial arterial blood specimens while the patient was breathing 90% oxygen. All gas and blood specimens were analyzed with a CIBA-Corning model No. 288 blood gas system (CIBA-Corning, Medfield, Massachusetts) on a day when the barometric pressure was 752 mm of mercury and the patient's temperature was 37°C (98.6°F). The partial pressures of oxygen in the gas from the chest tubes, abdominal drain, and arterial blood are shown in Table 1.

A complete workup—including routine bacterial and acid-fast bacillary cultures; serologic tests for Goodpasture's syndrome, Wegener's granulomatosis, and systemic lupus erythematosus; bronchoscopy; and open-lung biopsy—failed to reveal the cause of the patient's respiratory and renal failure. A renal biopsy revealed nonspecific immune complex-mediated disease, and the only positive serologic test was for hepatitis B surface antigen. The patient continued to deteriorate, and *Candida* species sepsis developed, necessitating support with dopamine and amphotericin B. The patient died on the 18th hospital day, and permission for an autopsy was not granted.

TABLE 1.—*Measurements of Partial Pressure of Oxygen in a 60-Year-Old Patient With Tension Pneumoperitoneum*

Site	*Partial Pressure of Oxygen, mm of mercury*
Chest tube #1	627
Chest tube #2	633
Abdominal drain	632
Radial artery	67

Discussion

Tension pneumoperitoneum from a grenade-induced gastric perforation was first reported in 1917 by Oberst, a German physician.[1] He postulated that a valvular mechanism, possibly caused by the liver overlying a perforation in the stomach, allowed air into but not out of the intraperitoneal cavity. A massive accumulation of free air would result in elevation of the diaphragm, with a consequent restriction of lung volumes and a decrease in venous return, causing hemodynamic instability. Studies in dogs have shown that an elevation of intra-abdominal pressures leads to a reduction in cardiac output, stroke volume, and arterial Po_2 and an increase in systemic vascular resistance.[2,3]

Abdominal fullness and dyspnea usually occur with tension pneumoperitoneum. The findings of a physical examination are notable for a grossly distended, barrel-shaped abdomen, although this finding may be masked in morbidly obese persons. Bowel sounds are usually present but distant, and tenderness is minimal unless peri-

TABLE 2.—*Causes of Tension Pneumoperitoneum Reported in the Literature*

Reference	*Cases, No.*	*Source*	*Cause*
Lagundoyle and Itayem, 1970[20]	2	Gastrointestinal	Abdominal-pelvic tuberculosis; puerperal sepsis, abscess
Hall, 1971[17]	2	Gastrointestinal	Colostomy leak
Thiele, 1973[30]	2	Gastrointestinal	Compressed air injury of colon
Echave et al, 1975[14]	1	Gastrointestinal	Duodenal ulcer perforation
Ogg and Davidson, 1975[24]	1	Gastrointestinal	Perforation from EGD
Addison and Broughton, 1976[11]	4	Gastrointestinal	Cecal perforation from pseudo-obstruction; perforation from sigmoid cancer (2 cases); duodenal ulcer perforation
Irwin, 1976[19]	1	Gastrointestinal	Ileocolic anastomosis leak
Linch et al, 1979[22]	1	Gastrointestinal	Gastric perforation from CPR
Gimmon et al, 1980[16]	1	Gastrointestinal	Ischemic colitis
Hutchinson et al, 1980[8]	1	Gastrointestinal	Gastric perforation from aerophagia
Taub et al, 1980[29]	1	Gastrointestinal	Gastric ulcer perforation with EGD
Roberts et al, 1981[26]	1	Gastrointestinal and pulmonary	Traumatic gastric perforation with mechanical ventilation
Mills et al, 1983[23]	1	Gastrointestinal	Gastric rupture from CPR and esophageal intubation
Olinde et al, 1983[5]	1	Gastrointestinal	Gastric ulcer perforation
Ehrlich et al, 1984[15]	1	Gastrointestinal	Perforation from colonoscopy
Ballet and Michel, 1985[12]	1	Gastrointestinal	Oxygen flow into nasogastric tube
Biert et al, 1987[9]	1	Gastrointestinal	Gastric perforation from aerophagia
Higgins et al, 1988[18]	1	Gastrointestinal	Ileorectal anastomosis with aerophagia
Ralston et al, 1989[25]	1	Pulmonary	Mechanical ventilation
Yip et al, 1989[32]	1	Urinary tract	Bladder catheter left open to air
Cameron et al, 1991[6]	1	Gastrointestinal	Gastric rupture from CPR
Yip et al, 1991[31]	1	Gastrointestinal	Colonic perforation from polypectomy
Barnett et al, 1992[13]	1	Gastrointestinal	Cecal perforation from colonoscopy
Winer-Muram et al, 1993[7]	2	Pulmonary	Mechanical ventilation
Critchley and Rowbottom, 1994[10]	1	Pulmonary	Mechanical ventilation
Schwarz et al, 1994[27]	2	Pulmonary	Mechanical ventilation
Serdyn and Lake, 1994[28]	1	Gastrointestinal	Gastric ulcer perforation
Lal et al, 1995[21]	1	Pulmonary	Tracheal tear, mechanical ventilation

CPR = cardiopulmonary resuscitation, EGD = esophagogastroduodenoscopy

toneal inflammation is also present.[4] Evidence of increased intra-abdominal pressure, such as rectal prolapse, may be present, as may crepitus due to subcutaneous air in the abdominal wall.[5] Examination of the lower extremities and genitals may reveal signs of venous congestion, such as edema and, in one reported case, priapism.[6] Pelvic vein thrombosis has been reported with tension pneumoperitoneum.[7] Acute aortic occlusion is another possible complication, with the loss of pulses, sensation, and motor function in the lower extremities.[5] As the pneumoperitoneum progresses, the patient may become hypotensive, tachycardic, and cyanotic and may suffer cardiac or respiratory arrest.[5,8-10]

We reviewed 36 reports of adult cases covering the past 25 years and found that the causes of tension pneumoperitoneum can be divided into gastrointestinal (27 cases), pulmonary (7 cases), a combination of gastrointestinal and pulmonary (1 case), and urologic causes (1 case).[5-32] Table 2 lists the more specific causes of or contributing factors to tension pneumoperitoneum. In more recent years, a growing number of cases of this disorder have been caused or exacerbated by positive-pressure ventilation. Air from a pneumothorax or pneumomediastinum can penetrate the diaphragm through normal apertures into the retroperitoneal space.[33] From there, it can rupture into the intraperitoneal cavity. Other causes of tension pneumoperitoneum include endoscopy (both esophagogastroduodenoscopy and colonoscopy),[12,15,24,29,32] gastric or duodenal ulcer perforation,[5,11,14,28,29] aerophagia or air insufflation of the gastrointestinal tract,[8,12,30] and gastric rupture due to cardiopulmonary resuscitation.[6,22,23] An unusual case of tension pneumoperitoneum occurred in a woman with transitional cell carcinoma of the bladder who had a Foley catheter inserted that was left open to the air.[32]

The diagnosis of tension pneumoperitoneum is based on clinical signs and an abdominal radiograph showing intraperitoneal gas with upward displacement of the diaphragm and medial displacement of the liver ("saddlebag sign").[8] The cause of the tension pneumoperitoneum may not be immediately apparent. If perforation of the gastrointestinal tract is suspected, exploratory laparotomy may be warranted. In mechanically ventilated patients, however, a search should be done for accompanying signs of barotrauma, such as pneumothorax, pneumomediastinum, or subcutaneous emphysema. In a review of 28 cases of pneumoperitoneum (though not necessarily due to tension) associated with mechanical ventilation, 27 patients had other signs of barotrauma.[33] Tension pneumoperitoneum caused by barotrauma is also usually associated with high peak end-expiratory pressures and tidal volumes.[33] We describe a simple test, done once before by Ralston, that clearly demonstrates the source of the intraperitoneal gas.[25] We measured the partial pressure of oxygen in gas taken from the pleural and peritoneal

spaces and showed that it was the same as that expected in the trachea and was far greater than that expected in ambient air. The results of this test enabled us to determine with certainty that the source of the intraperitoneal gas causing tension pneumoperitoneum in our patient was from the lung, and an unnecessary laparotomy was avoided. The only gastrointestinal source that could practically cause a tension pneumoperitoneum with similar Po_2 measurements in gas specimens would be a tracheoesophageal fistula, but there was no evidence of gastrointestinal dilatation in our patient.

Regardless of the cause, the emergent treatment of tension pneumoperitoneum in an unstable patient should be percutaneous catheter insertion or, if time permits, drain placement to relieve the intraperitoneal pressure. This maneuver usually results in immediate hemodynamic and ventilatory improvement.* Thereafter, treatment depends on the specific cause. Although laparotomy may be necessary if a gastrointestinal cause is suspected, a surgical procedure should be avoided if the gas has dissected into the peritoneal cavity from the lungs. Patients with tension pneumoperitoneum due to pulmonary barotrauma may require continuous intraperitoneal catheter drainage for the duration of positive-pressure ventilation.

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Wegener's Granulomatosis Presenting as Dilated Cardiomyopathy

JOHN D. DAY, MD
KRISTIN E. ELLISON, MD
INGELA SCHNITTGER, MD
MARK G. PERLROTH, MD
Stanford, California

WEGENER'S GRANULOMATOSIS is characterized by necrotizing, vasculitic, granulomatous lesions of the kidneys and upper and lower respiratory tract. Clinically notable cardiac involvement with the disease process is only rarely encountered. We describe the case of a patient who initially presented with dilated cardiomyopathy and who was later found to have elevated levels of antineutrophil cytoplasmic antibodies (c-ANCA); renal and pulmonary biopsy findings were consistent with Wegener's granulomatosis.

Report of a Case

The patient, a 57-year-old woman, presented with dyspnea on exertion and paroxysmal nocturnal dyspnea for two years. Eighteen months after her symptoms started, she was noted to have proteinuria and mild renal insufficiency. In July 1995, she underwent a cardiac evaluation

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From the Division of Cardiology, Department of Medicine, Stanford University Medical Center, Stanford, California.

Reprint requests to Mark G. Perlroth, MD, Stanford University Medical Center, Falk Research Center CV-263, 300 Pasteur Dr, Stanford, CA 94305-5246.

at an outside hospital for dyspnea on exertion after walking one block. An exercise stress test was stopped at stage I because she had severe shortness of breath. Dobutamine echocardiography showed global hypokinesis and four-chamber enlargement with possible apical and anteroapical ischemia. A subsequent coronary angiography was remarkable only for 30% to 40% stenosis of the proximal left anterior descending artery. A month later, she presented in pulmonary edema due to dilated cardiomyopathy and acute renal failure. At that time, her serum creatinine level was 430 μmol per liter (4.9 mg per dl), the hematocrit was 0.28 (27.9%), and a c-ANCA level was 18.6 equivalent units per ml (normal < 2.5). Her leukocyte count, creatine kinase, C3 complement, and C1 esterase levels were all within normal limits. A chest x-ray film showed cardiomegaly, pulmonary edema, and bilateral pleural effusions.

Echocardiography was repeated and was unchanged except for the new onset of a small pericardial effusion. A percutaneous renal biopsy showed crescentic glomerulonephritis without immune complex deposition, consistent with Wegener's granulomatosis. Of note, the patient had two episodes of supraventricular tachycardia, one described as multifocal atrial tachycardia and the other as atrial fibrillation, both of which responded to the intravenous administration of digoxin and diltiazem. She was discharged home on a regimen of diuretics, 1 mg per kg per day of oral cyclophosphamide, and 1 mg per kg per day of prednisone.

The patient did well at home for about a month until she presented to Stanford University Medical Center, Stanford, California, in September 1995 with increased dyspnea and worsening renal function. A chest radiograph showed cardiomegaly and focal areas of air-space disease throughout the right lung. The electrocardiogram was remarkable for left ventricular hypertrophy with repolarization abnormalities laterally. Echocardiography now showed worsened systolic function—ejection fraction, 0.20 (20%), as calculated by the ellipsoid-single plain method in the apical four-chamber view (Hewlett-Packard, Palo Alto, California, "Sonos Phased Array Imaging System Reference Guide," June 1994)—and moderate mitral regurgitation without any evidence of valvular vegetation. During this hospital stay, she was treated more aggressively for her Wegener's granulomatosis with intravenous cyclophosphamide, 2 mg per kg per day, and methylprednisolone sodium succinate. In addition, hemodialysis was started, with the placement of an arteriovenous fistula. A bronchoscopy with pulmonary biopsy was remarkable for grossly hemorrhagic alveoli, normal cytologic smears, and cultures negative for pathogens. She responded well to this regimen with a near return to normal mitral valve function, improved systolic function—ejection fraction, 0.30 (30%)—and pronounced symptomatic improvement.

Discussion

In this patient with Wegener's granulomatosis presenting as dilated cardiomyopathy, an endomyocardial biopsy was not done because of the low clinical yield of cardiac biopsies for diagnosing the cause of dilated cardiomyopathy.[1] Although histologic proof of myocardial involvement is lacking in this patient, the onset of congestive heart failure and renal involvement are temporally related. Moreover, global systolic function, as measured by echocardiography, appeared to decrease in conjunction with declining renal and pulmonary function after initial inadequate treatment of Wegener's granulomatosis. In addition to worsening global systolic function, mitral regurgitation developed in our patient, a finding not seen on two previous echocardiograms, which may be consistent with Wegener's granulomatosis-induced valvulitis or annular dilatation due to her dilated cardiomyopathy.[2-6] It is interesting to note that after more intensive therapy for Wegener's granulomatosis had been initiated, her systolic function improved and the mitral regurgitation nearly disappeared. This dramatic improvement of mitral valve function may be a result of treatment of the underlying Wegener's granulomatosis, as has been previously reported,[3] or of improved left ventricular function.

Since its initial description in 1931[7] and later confirmation in 1936,[8] Wegener's granulomatosis has been characterized histologically by necrotizing granulomatous vasculitis of the upper and lower respiratory tracts and the kidneys. Although the cause is unknown, the disease is generally considered a hypersensitivity disorder. It occurs most commonly in the fourth and fifth decades of life, with equal frequency among men and women. Wegener's granulomatosis usually develops over a 4- to 12-month period, with 90% of the patients presenting initially with upper or lower respiratory tract symptoms.[9-11] Although limited pulmonary forms of Wegener's granulomatosis have been described, renal involvement later in the disease process is nearly uniform.[12] The diagnosis of Wegener's granulomatosis in the past was made histopathologically, but the recent detection of characteristic circulating autoantibodies to neutrophil cytoplasmic antigens now permits earlier diagnosis and treatment.[13,14] Without treatment, the condition is usually fatal within a year of diagnosis. Despite the treatment-related morbidity, current therapy consisting of the use of glucocorticoids and cyclophosphamide allows complete remission in 75% of patients.[11]

In Wegener's initial paper describing the disease, he noted the possible involvement of the heart in the disease process.[8] Although subsequent autopsy studies have shown the heart to be involved frequently in Wegener's granulomatosis, clinical studies report the incidence of cardiac involvement as 8% to 12%.[10,11,15] The most common cardiac histopathologic findings reported are pericarditis and coronary arteritis in 50% of the patients, followed by focal myocarditis (25%), valvulitis or endocarditis (21%), conduction system defects (17%), and myocardial infarction (11%).[15]

In a 1980 histopathologic review of 27 case reports of cardiac involvement of Wegener's granulomatosis, 7 of the cases (26%) had evidence of focal myocarditis at autopsy.[15] Several reports exist where focal myocarditis led

to a clinical diagnosis of dilated cardiomyopathy. Of these rare reports, dilated cardiomyopathy was not found until after treatment with cyclophosphamide had been initiated.[4,10] In patients with bone marrow transplantation where much higher doses of cyclophosphamide are used, dilated cardiomyopathy may result from cyclophosphamide toxicity.[16,17] To our knowledge, this is the first case of Wegener's granulomatosis described in which the patient originally had dilated cardiomyopathy.

Unfortunately for our patient, even though the Wegener's granulomatosis was diagnosed, she was not adequately treated with corticosteroids and cyclophosphamide. Thus, over the month following diagnosis, her cardiac function declined further, manifested by a worsening ejection fraction and mitral regurgitation, extensive pulmonary involvement, and the need for lifelong hemodialysis. This case shows that although the clinical manifestation of cardiac disease in Wegener's granulomatosis is not usually encountered, it should be considered in the differential diagnosis of dilated cardiomyopathy in a patient with newly occurring pulmonary, renal, or other multisystem disorders.[18]

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Topics in Primary Care Medicine

Prophylaxis Against Opportunistic Infections in Patients Infected With the Human Immunodeficiency Virus

LAURA W. CHEEVER, MD; RICHARD E. CHAISSON, MD; *and*
JOEL E. GALLANT, MD, MPH, *Baltimore, Maryland*

The prevention of opportunistic infections has become one of the most important components in the care of patients infected with the human immunodeficiency virus (HIV). The progression of HIV infection to advanced cellular immune incompetence predictably increases the risk of specific opportunistic infections. As host defenses wane, the likelihood of infections rises, first with more virulent pathogens such as *Streptococcus pneumoniae* and *Mycobacterium tuberculosis*, then with the true opportunists such as *Pneumocystis carinii* and cytomegalovirus (CMV). The probability of an infection occurring depends on the interplay of host immunity, pathogen prevalence and virulence, and the use of prophylaxis. The efficacy of prophylaxis for *P carinii* pneumonia was demonstrated early in the acquired immunodeficiency syndrome (AIDS) epidemic, and it has since been found to improve survival and slow the progression of HIV disease.[1-3] This success of *P carinii* pneumonia prevention has encouraged research on prophylaxis against other opportunistic infections. The introduction of new preventive therapies to the standard care of patients with HIV depends on their efficacy, tolerability, convenience, cost, and effects on quality of life. Detailed recommendations for preventing opportunistic infections were recently published by the United States Public Health Service (USPHS) and the Infectious Diseases Society of America (IDSA).[4] In this review, we will consider current strategies for the prevention of opportunistic infections in adult patients with HIV infection. Preventing opportunistic infections in children with HIV infection is considered elsewhere.[4]

Pneumocystis carinii Pneumonia

Pneumocystis carinii pneumonia is the most common serious opportunistic infection among patients with AIDS in the United States. This pneumonia will develop eventually in at least 75% of HIV-infected patients in the absence of prophylaxis. The risk of infection increases with decreasing CD4 counts. The Multicenter AIDS Cohort study found that HIV-infected patients with CD4 counts of 201 to 350 $\times$ 10^6 per liter (201 to 350 per mm^3) had a 4.0% incidence of *P carinii* pneumonia within a year, whereas the incidence was 44.4% among those with CD4 counts of less than 100 $\times$ 10^6 per liter.[5,6] Patients with a history of *P carinii* pneumonia have a recurrence rate of 70% within a year in the absence of prophylaxis.[7] Because *P carinii* pneumonia is so common and because the mortality rate is 15% to 20% per episode,[8] prophylaxis is imperative for patients at risk for the disease. The USPHS-IDSA guidelines recommend prophylaxis for patients with a history of *P carinii* pneumonia; those with CD4 counts of less than 200 $\times$ 10^6 per liter; and patients with unexplained temperatures of greater than 37.8°C (100°F) for more than two weeks or oropharyngeal candidiasis, which have been associated with an increased risk of *P carinii* pneumonia irrespective of the CD4 count.[9] Three prophylactic regimens are currently widely used: the combination drug of trimethoprim and sulfamethoxazole, dapsone, and aerosolized pentamidine isethionate.

Trimethoprim and Sulfamethoxazole

The combination of trimethoprim and sulfamethoxazole is more than 95% effective in preventing *P carinii* pneumonia when patients adhere to therapy.[10] Several comparative trials have shown the use of trimethoprim-sulfamethoxazole to be superior to that of aerosolized pentamidine for primary and secondary prophylaxis. In a randomized primary prophylaxis trial with an average follow-up of 8.8 months, none of 142 patients assigned to receive trimethoprim-sulfamethoxazole (either 1 single-strength or 1 double-strength tablet daily) had *P carinii* pneumonia develop compared with 6 of 71 (8.4%) patients assigned to receive aerosolized pentamidine isethionate (300 mg monthly).[11] In a randomized trial of secondary prophylaxis, the recurrence rate for *P carinii* pneumonia was 3.5% per year in patients receiving

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From the Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland.

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Reprint requests to Richard E. Chaisson, MD, Division of Infectious Diseases, Johns Hopkins University School of Medicine, 600 N Wolfe St, Carnegie 292, Baltimore, MD 21287-6220.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CMV = cytomegalovirus
HIV = human immunodeficiency virus
IDSA = Infectious Diseases Society of America
Ig = immunoglobulin
USPHS = United States Public Health Service

trimethoprim-sulfamethoxazole, one double-strength tablet daily, compared with 18.5% in patients receiving aerosolized pentamidine, 300 mg monthly.[12]

Trimethoprim-sulfamethoxazole also appears to be more effective than dapsone for primary prophylaxis. The AIDS Clinical Trials Group study 081 observed 842 patients an average of 39 months after randomization to receive either trimethoprim-sulfamethoxazole, one double-strength tablet twice a day; dapsone, 50 mg twice a day; or aerosolized pentamidine, 300 mg monthly.[10] In an intention-to-treat analysis, the number of episodes of *P carinii* pneumonia was about equal in each of the three groups. An analysis of assigned treatments at the time of *P carinii* pneumonia diagnosis, however, revealed that the use of trimethoprim-sulfamethoxazole was the most effective treatment. In those patients continuing their assigned regimen, *P carinii* pneumonia occurred at a rate of 1.2 episodes per person-year among patients taking trimethoprim-sulfamethoxazole, 2.6 episodes per person-year for patients taking dapsone, and 5.7 episodes per person-year for patients taking aerosolized pentamidine. In a study of intermittent therapy, the cumulative two-year incidence of *P carinii* pneumonia was 11% among patients assigned to receive dapsone, 100 mg, plus pyrimethamine, 50 mg, twice a week compared with 0% among patients assigned to take trimethoprim-sulfamethoxazole, one double-strength tablet twice per day three times a week.[13]

Side effects are common among patients taking trimethoprim-sulfamethoxazole and are often severe enough to require discontinuation of the drug. The most common of these are fever, rash, leukopenia, and nausea. In the AIDS Clinical Trials Group study 081, 51% of the patients receiving trimethoprim-sulfamethoxazole discontinued their treatment because of adverse effects.[10] The dose used in the study was two to four times the doses used in current practice, however, and adverse reactions to trimethoprim-sulfamethoxazole appear to be dose-dependent.[11] Oral desensitization to trimethoprim-sulfamethoxazole in patients with previous adverse reactions has been advocated by some clinicians.[14,15] The major toxic effects of trimethoprim-sulfamethoxazole are not mediated by immunoglobulin (Ig) E, however; thus, successful desensitization may merely reflect successful rechallenge with the agent because rechallenge at standard doses is tolerated by about half of patients with a history of mild drug reactions.[16] Comparative trials of rechallenge at full prophylactic dosages versus gradual dose escalation are needed to clarify this issue.

Trimethoprim-sulfamethoxazole is the preferred drug for *P carinii* prophylaxis. In addition to being the most effective agent, it appears to also protect against other opportunistic infections such as toxoplasmosis and infections with pyogenic bacteria.[12,17] The recommended dose is one double-strength tablet a day. Other regimens that appear to be effective include one single-strength tablet a day or one double-strength tablet three times a week.

Dapsone

Dapsone is now the second-line agent for *P carinii* pneumonia prophylaxis, with efficacy equal to or greater than aerosolized pentamidine.[10,18] As with trimethoprim-sulfamethoxazole, side effects are common, with about 42% of patients discontinuing dapsone because of adverse drug reactions.[10] These include rash, nausea, methemoglobinemia, and dose-related anemia. Severe hemolytic anemia may develop in patients with glucose-6-phosphate dehydrogenase deficiency, a condition that affects 11% of African Americans.[19] Patients of African-American and Mediterranean descent should have their glucose-6-phosphate dehydrogenase level checked before dapsone therapy is initiated. About 70% of patients who are intolerant to trimethoprim-sulfamethoxazole will tolerate dapsone.[20]

The minimal effective dose of dapsone for prophylaxis is not known. The USPHS-IDSA guidelines recommend using dapsone, 100 mg a day, the best-studied dose.[4] The use of dapsone, 100 mg per week, in combination with pyrimethamine was less effective than trimethoprim-sulfamethoxazole in preventing *P carinii* pneumonia,[13] and 50 mg a day was shown to be inferior to 100 mg a day.[10,18] As with trimethoprim-sulfamethoxazole, patients who are intolerant of higher doses of dapsone may tolerate lower doses.

Aerosolized Pentamidine Isethionate

Aerosolized pentamidine is the best alternative for patients intolerant of both trimethoprim-sulfamethoxazole and dapsone. The recommended regimen is 300 mg given monthly by the Respirgard II jet nebulizer. Because inhalation results in minimal systemic absorption, aerosolized pentamidine is well tolerated, with only 3% of patients discontinuing treatment because of adverse reactions.[11] The most common adverse reaction is cough and bronchospasm, especially in patients with a history of asthma. For such patients, pretreatment with an inhaled bronchodilator can improve tolerability.

In addition to lower prophylactic efficacy, there are several other drawbacks to the use of aerosolized pentamidine. It has been associated with atypical presentations of *P carinii* infection, including upper lobe infiltrates and extrapulmonary disease,[21,22] as well as pneumothorax.[23,24] Because of the potential for facilitating tuberculosis transmission, the Centers for Disease Control and Prevention recommends that aerosolized pentamidine be administered in areas with negative pressure ventilation and that patients be assessed for symptoms of tuberculosis at each visit.[25] Finally, the cost of pentamidine is $1,200 per year, not including the cost of administration, whereas trimethoprim-sulfamethoxazole and dapsone cost less than $50 per year.[26]

Other Regimens

Administering pentamidine intravenously, 4 mg per kg a month, was found to be effective in preventing *P carinii* pneumonia in a case series of 52 patients.[27] There was one case of pneumocystosis in 587 patient-months of prophylaxis. Likewise, in a case series of 96 patients receiving intramuscular pentamidine (4 mg per kg up to 300 mg a month), there were only 3 cases of *P carinii* pneumonia in 776 months of patient follow-up.[28] In both studies, however, patients had adverse reactions commonly associated with the use of parenteral pentamidine, including hypotension and hypoglycemia. Given the substantial adverse reactions and lack of controlled trials, the use of parenteral pentamidine is not currently recommended for *P carinii* prophylaxis.

Atovaquone, clindamycin and primaquine phosphate in combination, trimethoprim and dapsone in combination, and pyrimethamine and sulfadiazine in combination have been used as prophylactic regimens but are not recommended for routine use until further data are available. The suspension of atovaquone has substantially better bioavailability than the previously available tablet formulation and is being studied for use as a prophylactic agent.

Toxoplasmosis

Toxoplasmic encephalitis in patients with AIDS is usually a result of the reactivation of latent infection. Thus, patients who are seronegative for anti-*Toxoplasma* IgG are at low risk for disease.[29] In the United States, anti-*Toxoplasma* seropositivity ranges from 10% to 40%, and encephalitis will eventually develop in a third of IgG-positive HIV-infected patients.[30] Prophylaxis is therefore targeted at patients who are seropositive for anti-*Toxoplasma* IgG and are sufficiently immunosuppressed for toxoplasmic encephalitis to develop, usually when the CD4 counts are less than 100×10^6 per liter.

Trimethoprim-sulfamethoxazole appears to be the most effective drug in preventing the reactivation of toxoplasmosis. In a retrospective study of patients on *P carinii* pneumonia prophylaxis, toxoplasmosis did not develop in any of the 60 patients taking trimethoprim-sulfamethoxazole (1 double-strength tablet twice a day, 2 days per week) compared with 12 of 95 (13%) taking pentamidine ($P = .014$).[31] Toxoplasmosis developed in 33% of patients on pentamidine therapy who were seropositive for *Toxoplasma gondii*. Similarly, in a prospective study of *P carinii* pneumonia prophylaxis comparing the use of trimethoprim-sulfamethoxazole with that of pentamidine, only 1 of 10 cases of toxoplasmosis occurred in patients receiving trimethoprim-sulfamethoxazole.[12] In a European trial of antiretroviral therapy in which 73% of patients were seropositive for *T gondii*, toxoplasmic encephalitis developed in only 1 of 80 (1.3%) patients taking trimethoprim-sulfamethoxazole, compared with 30 of 228 (13.2%) taking aerosolized pentamidine ($P = .002$).[32]

Dapsone with pyrimethamine also appears to be effective in preventing toxoplasmosis. In a randomized study of trimethoprim-sulfamethoxazole (2 double-strength tablets 3 times a week) compared with dapsone (100 mg a week) plus pyrimethamine (25 mg a week), toxoplasmosis occurred in 2 of 81 (2.5%) patients on trimethoprim-sulfamethoxazole therapy compared with 3 of 85 (3.5%) patients on a regimen of dapsone and pyrimethamine.[33] In another prophylaxis trial in an area highly endemic for toxoplasmosis, the disease developed in 5 of 173 (2.9%) patients receiving dapsone (50 mg a day) and pyrimethamine (50 mg a week) compared with 28 of 176 (15.9%) patients receiving aerosolized pentamidine.[34]

Of other agents studied for prophylaxis, pyrimethamine alone was ineffective,[35,36] and its use was associated with increased mortality in one study.[37] Clindamycin prophylaxis produced unacceptably high rates of diarrhea and rash.[38] Other regimens requiring further study include atovaquone, dapsone as a single agent, azithromycin, and clarithromycin. Patients who have had active toxoplasmic encephalitis require lifelong suppression.[30]

The USPHS-IDSA guidelines recommend that patients with anti-*Toxoplasma* IgG antibodies and CD4 counts of less than 100×10^6 per liter receive trimethoprim-sulfamethoxazole, one double-strength tablet daily.[4] Patients who cannot tolerate this regimen should receive dapsone, 50 mg a day, and pyrimethamine, 50 mg a week, with leucovorin calcium, 25 mg a week, to decrease hematologic toxicity. It is not known whether lower doses of leucovorin would be as effective in preventing pyrimethamine toxicity. Patients seronegative for anti-*Toxoplasma* IgG antibodies should avoid eating undercooked meat and should take precautions when handling cat feces to prevent infection with *T gondii*.

Mycobacterium tuberculosis Infection

Persons infected with HIV are at increased risk for active tuberculosis developing. These patients have a 2% to 10% yearly risk of the reactivation of latent infection.[39] Patients infected with HIV are also at increased risk for active disease as a result of primary infection.[40] Prophylaxis with isoniazid has been shown to decrease the incidence of active tuberculosis and improve survival in HIV-infected patients in areas endemic for tuberculosis.[41] In a randomized trial in Haiti, patients assigned to receive isoniazid, 300 mg a day, and pyridoxine, 50 mg a day, for 12 months had an 80% reduction in the incidence of tuberculosis and increased survival compared with controls assigned to receive vitamin B_6 only.[41] Taking isoniazid daily for six months resulted in a 60% decrease in the prevalence of active tuberculosis in a similar study in Zambia.[42]

Isoniazid prophylaxis is recommended for any HIV-infected person who meets one of the following criteria: a positive purified-protein derivative skin test (≥5 mm of induration), a history of a positive skin test without previous prophylaxis, or recent close contact with a person with active tuberculosis. The USPHS-IDSA guidelines recommend the use of isoniazid, 300 mg a day, for 12 months, supplemented with pyridoxine, 50 mg a day.[4,43] Alternatively, isoniazid can be given as observed therapy twice a week (15 mg per kg up to 900 mg). Six months of therapy may suffice, but further studies are needed. For patients intolerant to isoniazid, taking rifampin, 600 mg a day for 3

to 12 months, is effective.[44] Rifabutin is being studied as an alternative to isoniazid for tuberculosis prophylaxis.

Persons with HIV infection and cutaneous anergy may be at increased risk of tuberculosis developing.[45,46] The value of routine anergy testing is unclear, however, because of the inconsistency of anergy testing over time and the lack of association of anergy with the risk of tuberculosis in some studies. Currently the USPHS-IDSA guidelines call for an individualized use of anergy testing.[4] The efficacy of isoniazid chemoprophylaxis in anergic HIV-infected patients has not been established.

Mycobacterium avium Complex

Without prophylaxis, a large proportion of HIV-infected patients may have disseminated *Mycobacterium avium* complex, usually in late-stage disease after the CD4 count has fallen below 50×10^6 per liter.[47] Disseminated *M avium* complex is associated with fever, weight loss, decreased quality of life, and increased mortality.[48,49] Treatment of the disease usually requires lifelong combination therapy.

The combined data from two identical double-blind studies comparing the use of rifabutin, 300 mg a day, with that of placebo in patients with AIDS and a CD4 count of less than 200×10^6 per liter showed that bacteremia developed in 48 of 566 (8%) patients assigned to receive rifabutin and 102 of 580 (18%) patients assigned to receive placebo during a mean follow-up of 205 days.[50] Persons assigned to receive rifabutin had a delayed onset of fatigue and fever, as well as a decreased incidence of hospitalization, a decline in the hemoglobin level, and a decline in the Karnofsky score. Fewer deaths occurred in patients taking rifabutin—33 of 566 (5.8%) compared with 47 of 580 (8.1%); the difference was not statistically significant, however. Recent long-term follow-up data suggest that the use of rifabutin prolongs survival.[51] Therapy was discontinued because of adverse events in 16% of patients receiving rifabutin and 8% of placebo recipients. Rash, gastrointestinal distress, and neutropenia were the most commonly noted.

Uveitis has occurred with the administration of rifabutin at higher doses, and it has been reported in several patients receiving rifabutin for prophylaxis at the recommended dose of 300 mg a day.[52] Most patients with rifabutin-associated uveitis were also receiving fluconazole, which is known to increase rifabutin concentrations.[53] Rifabutin induces hepatic microsomal enzymes, which can affect the metabolism of many drugs including oral contraceptives, warfarin sodium, phenytoin (Dilantin), methadone, zidovudine, and saquinavir mesylate. *Mycobacterium avium* complex organisms from patients taking rifabutin in whom bacteremia develops do not show notable resistance to rifabutin.

Clarithromycin has also been studied as a prophylactic agent for *M avium* complex infection. In a multicenter trial comparing the use of clarithromycin, 500 mg twice a day, with that of placebo, treated patients had a 68% decrease in the incidence of bacteremia ($P < .001$) and a 30% decrease in mortality ($P = .016$).[54] In this trial, however, 58% of the breakthrough organisms were resistant to clarithromycin, the most important drug in the treatment of disseminated *M avium* complex.

The initial results of two recently reported trials find both clarithromycin and azithromycin more effective than rifabutin for *M avium* prophylaxis.[55,56] Both these studies also found the combination of rifabutin with either clarithromycin or azithromycin to be more efficacious than monotherapy with any agent. In addition, the rates of macrolide resistance in breakthrough organisms was considerably lower than previously reported. Because the use of rifabutin is not recommended for patients taking protease inhibitors, macrolides may become the preferred agents for *M avium* prophylaxis.

The USPHS-IDSA guidelines recommend that prophylaxis with rifabutin, 300 mg a day, be considered in patients with CD4 counts of less than 75×10^6 per liter.[4] Clarithromycin, 500 mg twice a day, or azithromycin dihydrate, 1,200 mg weekly, are effective alternatives and are recommended for patients taking protease inhibitors. All patients should be assessed before prophylaxis is instituted to ensure they do not have active tuberculosis, and a blood culture should be done to rule out the presence of disseminated *M avium* complex.

Fungal Prophylaxis

The occurrence of fungal infections increases dramatically as CD4 counts decline. The most serious of these, cryptococcal meningitis, affects 8% to 15% of patients with AIDS, usually when the CD4 count is less than 50×10^6 per liter.[57] Mucocutaneous candidiasis occurs in more than 90% of patients, with *Candida* species esophagitis affecting more than 15% of patients.[57] Endemic mycoses, such as histoplasmosis and coccidioidomycosis, affect 15% to 25% of patients from endemic areas.[57,58] Although the incidence of cryptococcal disease is relatively low, the morbidity and mortality associated with cryptococcosis make it a possible target for prophylaxis.

Fluconazole was effective in preventing serious fungal infections in one controlled clinical trial (AIDS Clinical Trials Group study 981). In this trial, 428 patients with CD4 counts of less than 200×10^6 per liter were randomly assigned to receive fluconazole (200 mg a day) or clotrimazole troches (10 mg 5 times a day).[59] Invasive fungal infections occurred in 9 of 217 patients (4%) assigned to receive fluconazole, compared with 23 of 211 patients (11%) assigned to receive clotrimazole ($P = .02$). The proportion of patients with cryptococcosis was 1% in the fluconazole-treated group and 7% in the clotrimazole-treated group ($P = .004$). Similarly, *Candida* species esophagitis occurred in 1% and 8% of patients in the two groups, respectively ($P = .004$). The benefit was most pronounced among patients with CD4 counts of less than 50×10^6 per liter. There was no difference in mortality between the two groups. An earlier study of patients given fluconazole at a dose of 100 mg a day found a protective effect against cryptococcal disease compared with historical controls.[60]

The most important drawbacks to routine antifungal prophylaxis are cost, drug interactions, and the potential for promoting infection with fluconazole-resistant *Can-*

TABLE 1.—*Prevention of Opportunistic Infections—Antimicrobial Prophylaxis*

Pathogen	*Indicotions for Prophyloxis*	*Regimens*
Pneumocystis carinii pneumonia....	Previous *P carinii* pneumonia; CD4 <200 × 10^6/liter; unexplained fevers >2 wk; oropharyngeal candidiasis	Preferred regimen: TMP-SMX, 1 double-strength (DS) tablet/day Alternatives: • TMP-SMX, 1 single-strength (SS) tablet/day or 1 DS 3×/wk • Dapsone, 100 mg/day • Dapsone, 50 mg/day, + pyrimethamine, 50 mg/wk, + leucovorin, 25 mg/wk • Dapsone, 200 mg/wk, + pyrimethamine, 75 mg/wk, + leucovorin, 25 mg/wk • Aerosolized pentamidine, 300 mg/mo
Toxoplasmosis	CD4 <100 × 10^6/liter and anti-*Toxoplosmo* IgG antibody	Preferred regimen: TMP-SMX, 1 DS/day Alternatives: • TMP-SMX, 1 SS/day, or 1 DS 3×/wk • Dapsone, 50 mg/day, + pyrimethamine, 50 mg/wk, + leucovorin, 25 mg/wk
Mycobocterium tuberculosis	PPD positive (≥ 5 mm induration); previous positive PPD untreated; high-risk exposure	Preferred regimen: isoniazid, 300 mg/day, + pyridoxine, 50 mg/day for 12 mo Alternatives: • Isoniazid, 15 mg/kg (up to 900 mg) 2×/wk, + pyridoxine, 50 mg 2×/wk, directly observed therapy, for 12 mo • Rifampin, 600 mg/day for 3-12 mo
Mycobocterium ovium complex	CD4 <75 × 10^6/liter	Rifabutin, 300 mg/day Clarithromycin, 500 mg 2×/day Azithromycin, 1,200 mg/wk
Serious fungal infections.....	Consider in patients with CD4 <50 × 10^6/liter	Preferred regimen: fluconazole, 200 mg/day
Cytomegalovirus (CMV).....	Consider in patients with CD4 <50 × 10^6/liter, anti-CMV IgG, and positive blood PCR	Preferred regimen: ganciclovir, 1,000 mg orally 3×/day
Bacterial infections	All patients	23-valent pneumococcal polysaccharide vaccine, 0.5 ml intramuscularly

IgG = immunoglobulin G, PCR = polymerase chain reaction, PPD = purified-protein derivative, TMP-SMX = trimethoprim-sulfamethoxazole

dida species. Such infection appears to be associated with a prolonged or early use of fluconazole,[61] and patients with fluconazole-resistant mycoses may require long-term therapy with intravenous amphotericin B. The cost to prevent a single case of invasive mycosis if all HIV-infected patients with CD4 counts of less than 200 × 10^6 per liter were given fluconazole, 200 mg a day, has been estimated to be $100,000.[59] Although fluconazole is generally well tolerated, about 15% of patients will have associated abdominal pain or nausea.[59]

Antifungal prophylaxis may be considered for patients at greatest risk for cryptococcal meningitis (CD4 count <50 × 10^6 per liter). Other considerations in prescribing antifungal prophylaxis include possible drug interactions, the complexity of medication regimens, and compliance. Long-term fluconazole therapy is indicated for patients with recurrent candidal esophagitis or with a history of treated cryptococcal meningitis. To date there is insufficient evidence to support the use of primary prophylaxis for histoplasmosis or coccidioidomycosis for patients from endemic areas. Studies are under way to determine the efficacy of intermittent high-dose fluconazole prophylaxis (such as 1,200 mg a week).

Cytomegalovirus Infection

As much as 90% of AIDS patients at autopsy have evidence of active CMV infection,[62] and sight- or life-threatening infections may develop in as much as 40% of patients as they become immunosuppressed and CD4 counts fall below 100 × 10^6 per liter.[63,64] Given the sight-threatening morbidity associated with CMV, the toxicity and expense of parenteral treatment, and the inability to maintain effective permanent remission in most patients, CMV disease is an appropriate target for prophylaxis.

Acyclovir is ineffective in preventing CMV disease in HIV-infected patients.[65] Preliminary analysis of a randomized trial of oral ganciclovir (1,000 mg 3 times a day) showed a 50% reduction in the incidence of CMV disease in the treated group.[66] Oral ganciclovir prophylaxis does not appear to affect ganciclovir susceptibility of the viral organisms that cause breakthrough disease.[67] A second trial of oral ganciclovir prophylaxis for CMV disease did not find a benefit.[68] The latter study did not include active monitoring for retinitis, however, and a large proportion of patients were crossed over to receive open-label oral ganciclovir.

Indications for oral ganciclovir prophylaxis remain to be determined. Targeting prophylaxis to patients with CD4 counts of less than 50 × 10^6 per liter and positive blood CMV polymerase chain reactions may be the most effective approach. To prevent infection, patients without serologic evidence of previous CMV infection should receive only CMV-negative blood products when transfusions are required.

Bacterial Infections

Infections with common bacterial pathogens occur with increased frequency in HIV-infected persons. These include *Streptococcus pneumoniae, Haemophilus influenzae, Pseudomonas aeruginosa,* and *Salmonella* species. Trimethoprim-sulfamethoxazole, used for the prophylaxis of *P carinii* pneumonia, has been shown to decrease the incidence of serious bacterial infections by 50% compared with aerosolized pentamidine.[12] The 23-valent polysaccharide vaccine is recommended by the USPHS-IDSA for all HIV-infected patients.[4] The efficacy of pneumococcal vaccine for patients with HIV and CD4 counts of greater than 200 × 10^6 per liter has recently been sug-

gested in a case-control study.[69] The vaccine should be given as early as possible in the course of illness to maximize the likelihood of an immune response. Vaccination against *H influenzae* type b is not routinely recommended as most strains of *Haemophilus* infecting adults are non–type b strains. Administering azithromycin and clarithromycin, given for *M avium* prophylaxis, also reduces the incidence of bacterial infections, particularly respiratory tract disease.[56,55]

Further Considerations Regarding Prophylaxis

Several therapies prevent or delay opportunistic infections in patients with HIV infection (Table 1). Clearly, prophylaxis against *P carinii* pneumonia is essential for patients with AIDS. Prophylaxis against toxoplasmosis and disseminated *M avium* complex also appears to be important in susceptible patients, and CMV disease and serious fungal infections are also preventable. The overall effect of patients taking several drugs for prophylaxis has not been established, however. Polypharmacy is often complicated by drug interactions and poor patient compliance. As noted previously, patients taking rifabutin and fluconazole may have a rise in serum rifabutin concentrations that may increase the rates of adverse drug effects. Administering rifabutin and clarithromycin decreases serum concentrations of zidovudine,[70,71] which may reduce the benefit of this antiretroviral agent. Thus, although there are many prophylactic agents available with proven efficacy, clinicians must tailor each patient's regimen and remain aware of new information regarding the overall efficacy of complex regimens. Future regimens, it is hoped, will combine broad efficacy against possible pathogens with acceptable toxicity, drug interactions, and cost.

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Commentary

Caution: The Meter Is Running

Informing Patients About Health Care Costs

MICHAEL S. WILKES, MD, PhD, *and* DAVID L. SCHRIGER, MD, MPH, *Los Angeles, California*

A 42-year-old mechanical engineer was recently laid off by a major defense contractor in southern California. He was unable to afford COBRA health insurance, not to mention support his family and pay the mortgage on their home. The man was brought to the emergency department with chest pain that was neither classic for myocardial ischemia nor easily attributable to a noncardiac cause. His electrocardiogram and the findings of a physical examination were normal. Other than his sex and a brother who, at the age of 53, had a heart attack, he had no risk factors for coronary artery disease.

What should be done for this man? With the exception of efforts in Oregon,[1] there has been a reluctance on the part of policy makers to engage in discourse on the merits of providing specific health care services in relation to the costs of these services. The avoidance of this topic reflects our societal discomfort with issues that directly link health care activities and cost and that necessarily bring to focus conflicts between individual and societal well-being. By both active and passive mechanisms, we try to maintain the illusion that we can make intelligent health care choices without considering their costs.

We explore the theoretical and practical considerations of whether health care professionals should routinely inform patients about the financial costs of their care. Our goal is to stimulate thought and discussion about the subject. Our premise is that to the extent we avoid explicitly dealing with these questions, we limit our capacity to improve our health care system and our society's overall health.

In the case of the engineer, even if practitioners could accurately predict the probability of this specific patient having an untoward event, this information would not dictate the proper disposition of this patient. When should a patient with chest pain and a normal electrocardiogram be admitted? When the probability of his having an episode of sudden death in the next 24 hours is 1 in 100,000, 1 in 1,000, or 1 in 10? The larger the denominator selected, the greater the total cost to society. Although the shape of the trade-off curve between risk and cost might be deduced by health care professionals or medical economists, logic and economic theory suggest that the public's health will be maximized only when it shares in the decision making.[2] Three questions arise that reach beyond medicine. First, what level of risk exclusion is best for society? Second, what level of risk exclusion is best for an individual? Third, what do we do when these points are not the same?

The opportunity to link health care services and costs need not be limited to public policy debate, but could occur every time a physician and patient must select among treatment alternatives. Returning to the case of the man with chest pain, the emergency physician was faced with deciding whether to admit the patient to the hospital or discharge him to home. Into this decision entered evidence from clinical research, the physician's past experience, medicolegal concerns, institutional policies, professional guidelines, and what the physician thought the patient wanted. In this case, the physician decided the safest treatment would be an admission to the coronary observation unit for one day to rule out a myocardial infarction. The patient was informed of the physician's decision and agreed to be admitted to the hospital. Because he had a possibly life-threatening condition that rendered him "nontransferable" to a public hospital, he was not given any financial information about the likely costs of his hospital admission or his responsibility to pay the bill. The man's hospital course was uneventful. It was determined that he had not suffered a myocardial infarction, and he was discharged to home 36 hours after admission. He did fine for several weeks—until the bill arrived, which he could not afford to pay. He was furious that he had not been given an estimate of the likely costs at the time of admission. The engineer argued that had he been told the low likelihood of an untoward event and that the hospital bill would likely exceed $3,000, he would not have agreed to being admitted.

From the patient's perspective, the hospital stay had some small benefits, namely ruling out a serious disease event and offering slight protection against sudden cardiac death. To him, however, the benefits did not outweigh the economic harm created by the cost of his hospital admission. The physician's perspective was dif-

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From the Division of General Internal Medicine and Health Services Research, Department of Medicine, and the Emergency Medicine Center, University of California, Los Angeles (UCLA), School of Medicine.

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ferent. He thought, "If I were this patient, I would want the hospitalization both for protection against sudden death and to make sure that I wasn't having a heart attack." The physician also considered the benefits to himself: "I don't want to risk getting sued for missing a myocardial infarction." This example illustrates how physicians and patients may have different estimates of the relative worth of health care activities.

Physician-Patient Communication

Over the past two decades, the physician-patient relationship has evolved from a primarily paternalistic model[3] to models that have been described as "informative," "interpretive," and "deliberative."[4] Not long ago, physicians typically shared little information with patients about their diagnosis or prognosis. They expected patients to be compliant, trustworthy, deferent, and to do what was needed to get well (as determined by the physician). Gradually physicians began to provide more information to patients about their diagnoses and the various options for evaluation and treatment. These shifts resulted from demands of a changing culture and a growing body of literature suggesting that for ethical, legal, and humanistic reasons, people should be provided with information about their illness and given an opportunity to make their own medical decisions.

Whereas most physicians attempt to adapt their interaction style to suit a patient and a particular situation,[5] they still maintain a paternalistic approach when it comes to financial aspects of health care. In our experience, physicians seldom take time to understand the economic effects of illness, testing, or hospitalization on a person or family, including such issues as time away from work and the effects of the cost of care on savings, debts, or general financial well-being. Even the best efforts to analyze the patient-physician interaction have failed to include cost as worthy of discussion.[4,6] When Eddy presented a model for how a health maintenance organization (HMO) might choose between low- and high-osmolarity contrast material for routine radiographic procedures, the responses were revealing.[7] In all letters to the editor, physicians said they would not expose their patients to the marginally more risky but substantially cheaper high-osmolarity agent, even if this decision would benefit society.[8-10] None of the authors even contemplated allowing patients to decide which agent was preferred.[11]

There are many possible reasons why physicians avoid discussing costs. Perhaps they are unfamiliar with actual net costs or the specifics of patients' insurance; perhaps they feel their job is to do what is best for the patient regardless of cost; perhaps physicians are uncomfortable being placed in a position where they need to allocate an important societal resource—namely, health services—or perhaps they simply feel they do not have the time to address these complicated issues.[5] Furthermore, some physicians may fear that patients who are provided with information on cost may make decisions that they will later regret. Whatever the reason, there is evidence that a patient's financial situation modifies decision making about a range of health issues.[12]

At the beginning of the century, physicians held a different place in society than they do today. Virtually all physicians served patients who had limited financial resources and no health insurance. They accepted payments that were congruent with the patients' ability to pay; often these payments were in services or materials rather than in money.[13] Because the little medical technology that existed was not costly, few medical decisions needed to be made in the context of cost.

The popularization of health insurance during the wage freezes of World War II and the subsequent establishment of Medicare and Medicaid created a system in which most patients were no longer fully responsible for the cost of their health care. Insured patients experienced few economic consequences of physicians' medical care decisions. Thus, there was no reason to disclose this information. Recent increases in the cost of health care have led insurance companies to alter policies so that large deductibles and copayments are commonplace. Furthermore, 37 million uninsured Americans are completely responsible for the cost of their care. Because most Americans are at least partly responsible for their medical bill, they are entitled to be told the economic consequences of their care. Even those enrolled in comprehensive managed care plans should be informed about the cost of care because their annual premium is necessarily linked to the membership's consumption of health care services.[14]

Different Perspectives

Despite the new financial vulnerability of patients, many practitioners still tacitly assume that "the patient has come to see me and therefore is willing to pay for the services, tests, and drugs that I deem appropriate to provide their care." If physicians were good proxies for their patients, there would be little need for financial disclosure because they would make the same decisions that patients would make. Observational evidence and theoretical arguments suggest that there are likely to be substantial differences between what physicians think patients want and what patients actually desire.[15]

How do physicians differ from their patients? First, they generally wield more power. They are members of the professional class and typically are among the most highly compensated members of society. Their daily immersion in the world of medicine makes them sophisticated consumers of health care. When ill, their experience with the health care system likely differs from that of their patients. For all of these reasons, physicians and patients may have divergent estimates of the ability of modern medicine to provide cures and comfort.

Second, the beliefs that led physicians to choose medicine as a career, the socialization process that takes place during medical school and residency training, and the tendency for professionals to value their life's work are likely to result in feelings and values about life, death, health, and the worth of medical care that differ

from those of the population at large.[16] Physicians generally value allopathic medicine above all other forms of health care, whereas patients may perceive other models of health and treatment as worthwhile.[17]

Third, consideration of medicolegal issues, knowledge and fear of rare events, and the desire to maintain or increase income may motivate physicians to provide a level of medical care that is often more extensive than patients want. Conversely, in capitated managed care, physicians may be so motivated to constrain costs that patients may end up receiving less care than is deserved. Recent cases reported in the press have demonstrated that often physicians are placed between the interests of a managed care organization and those of patients. In one typical case, a physician advised a patient that a procedure not covered by her insurance offered her the best hope of a cure (D. J. Rubsaman, *Professional Liability Newsletter*, 1995, vol 25, p 1). The physician initially assisted the patient in legal action designed to force the insurance company to pay for her care. The insurer then applied substantial pressure on the physician (through his immediate physician-supervisor) to alter his advice and to instead advise the patient that the procedure was not medically warranted. The physician complied. A successful lawsuit was initiated by the patient's estate.

This is not an isolated case. Many managed care organizations now routinely place a "gag clause" in their contracts with physicians, which prohibits physicians from disclosing to patients certain information. These contracts require that physicians place interests other than patient care at the forefront of their decision making. Making the disclosure of charges and options a routine part of medical care would help to restore physicians to the role of patients' advocates and facilitators and would make such gag clauses unenforceable on ethical and practical grounds.

Evidence supporting the hypothesis that physicians are not good proxies for their patients comes from studies showing that there are often wide disparities between a physician's perspective on an illness and the patient's[16,18] and that frequently physicians fail to consider factors that patients deem important in reaching a medical decision. External factors that may affect a patient's decision making may include the need to care for dependents, the need to show up at a job that could be lost for nonattendance, or other social or economic realities that preclude adhering to the course of action that the practitioner deems "ideal." Physicians may find it hard to empathize with a patient's predicament. If physicians do not know their patient's preference, they should simply ask.

A Clash of Perspectives

A 32-year-old female grocery store cashier went to a walk-in clinic for acute mild abdominal pain and nausea. The woman had health insurance with a $1,200 deductible. A physician whom she did not know took a complete history, including questions concerning her sexual activity and the use of contraceptives. The woman informed the physician that she had not been sexually active in more than a year and had regular periods. A physical examination revealed some mild tenderness in her left lower quadrant that the physician thought was consistent with constipation. He prescribed some medication and ordered some "blood tests."

A week later, the woman was feeling normal—until the bill arrived showing the cost of the visit to be $105 with a charge of $24 for a pregnancy test. She refused to pay for the laboratory test, explaining to her physician that at the time of her examination, she had clearly conveyed that there was no way she could be pregnant and that therefore a pregnancy test was pointless. She said that if she had been told the purpose of the blood test, she would have refused and accepted any risk that would result from a missed diagnosis of pregnancy. The woman felt that the physician had not trusted her and undervalued the importance of $24 to her budget.

The physician's explanation for ordering the test was that in his career, he had seen dozens of "immaculate conceptions," and he therefore felt justified spending $24 of the patient's money on a pregnancy test as part of his workup. The case remains in the hands of a collection agency.

The fundamental problem here, aside from poor communication, is that the patient and the physician each have estimated the benefits, harms, and net costs of doing the test, and their estimates—which are both accurate—differ. The patient estimates that the likelihood of pregnancy is zero; thus, there is no benefit, little harm, but high cost in doing the test. The physician recognizes that although the likelihood of this patient being pregnant is small—say, 1 in 1,000—there is a high likelihood that he will miss one such pregnancy during his career if he does not order pregnancy tests on patients like this. Thus, the benefit of ordering the test is that he protects himself from doing harm to a patient (missing a pregnancy). From his perspective, the only harm is that he may make his patient unhappy. Unless the care is capitated, it costs him nothing to obtain the test.

In this case, the physician approached the clinical decision from an epidemiologic perspective whereas the patient focused only on her particular circumstances. It would seem that the only way to remedy this situation is to disclose the option (to obtain a pregnancy test) and the physician's estimate of the benefits (small chance of detecting an occult pregnancy), harms (minute chance of false-positive or false-negative), and charge ($24) before the test is done. In this way, each patient can choose what he or she wants, satisfying the legal requirements of informed consent that assure the right to self-determination.[19]

Benefits of Disclosure

The main advantage of shared decision making in general, and the disclosure of charges in particular, is that patients then have an opportunity to make their own decisions, thus relieving practitioners from guessing what patients want. People who share responsibility for deci-

sion making are less likely to blame others when things go wrong and are more likely to experience a sense of control.[20] Although controversial, some research has shown that medical outcomes actually improve when patients are involved in the decision-making process.[21]

The main advantage to practitioners is that they are relieved of the responsibility of guessing what patients want. There are several ethical advantages to disclosure. In the current system, certain patients routinely receive direct financial information about their care. Persons with little or no health insurance are told "We do not accept Medicaid at this magnetic resonance imaging center, and the cost of the scan is $1,100,"[22] or "Your insurance status precludes admission to this hospital. We can either transfer you elsewhere or we need $5,000 in advance." Patients with insurance are rarely informed of such cost details. This is insurance "classism" and is unfair. It places the burden of the financial details on patients who can least afford it, while sparing those who have means. Until such time that a more just system of health insurance is instituted, physicians and administrators must take care to ensure that they are not biased in what information they share with patients.

Physician-patient discussions of costs need to be far more than a recitation of numbers. If done sensitively, such discussion often serves to further the physician-patient alliance. Helplessness and worry can be replaced by knowledge and control as physicians and patients work together to negotiate the best strategy for treatment.

An important theoretical advantage of the disclosure of costs is that it might better prepare the public to understand and participate in the planning of our health care system. As with many goods and services that are provided through an insurance pool, everyone wants to pay the least amount into the pool while getting the most out of it. Without disclosure, many consumers remain unaware of the amount of resources they are consuming. Not surprisingly, they are often shocked by the cost of health insurance and fail to see the relationship between the use of services and the cost of insurance. A policy of universal disclosure may eventually educate people about health care expenditures and help them appreciate the connections between their own health care use and health care planning on the national level. This, in turn, would make the public more receptive to policies that rate health coverage in the face of limited resources. Still another advantage is that it would make physicians more aware of costs and encourage them to consider explicitly the effectiveness-cost relationship of their actions, particularly for services that are of marginal value.

Harms of Disclosure

Although financial disclosure would likely be perceived as ethically beneficial in all but the paternalistic model of medical care, it cannot be recommended for all patients in all situations. For some patients, the burden of the knowledge outweighs its usefulness. Patients with acute treatable but life-threatening conditions (such as a ruptured aortic aneurysm) probably would not benefit from being informed of the likely cost of their care. Important issues also arise for severely mentally ill patients, those with pronounced cognitive impairment, and those in severe distress—when a surrogate would normally be called on for assistance. Should financial data be discussed with surrogates who may stand to benefit from a particular decision or to whom the patient might not wish confidential financial data be disclosed? And what about patients who are generally considered competent but who cannot understand the complex financial implications of medical treatments, say at the end of life? Should there be a different standard of competency for financial matters?[23,24]

For those who are emergently ill, but who do not fall into the aforementioned categories, the balance between the benefits and burdens of disclosure becomes hazy. Does a stable patient with an acute myocardial infarction need to know about financial matters, or will this information do nothing more than raise catechol levels and myocardial oxygen demand? It has been suggested that unwanted information has resulted in devastating health consequences,[25,26] but this has yet to be confirmed.

Certain patients who are not acutely ill may still find detailed financial information distasteful or burdensome. We must recognize that although it is currently fashionable to share medical information with patients, many patients make it clear that they do not want to be bothered with such information and prefer to leave decisions in the hands of their physicians. For such patients, financial disclosure may be harmful. One option is to offer patients four choices regarding cost information: to get all cost information, to get only charges for specific items about which they inquire, to get only information that the physician thinks is important, or to get no information at all.

Barriers to Disclosure

Even if physicians agree that disclosure is in patients' best interest, there are still barriers to disclosure. Given the complexity of different insurance plans, often neither physicians nor patients are familiar with the particulars of their own health insurance plans. Further, it is often difficult for people to arrive at the "best" decision based solely on probabilities and expected outcomes. The tension of the moment may hinder our ability to make a decision that is best for the long term. Further, physicians and patients may have difficulty adequately communicating information and feelings about matters regarding probabilities (how small is 1 in 5,000?) and future events ("how much pain will I be in during the postoperative period?"). Nevertheless, despite their difficulty and tendency to be time-consuming, discussions of expected benefits and harms are valuable, and for major decisions they have been institutionalized in the formal informed consent process.

Another practical barrier to financial disclosure is its costs in time and money. In the pregnancy-test case that we considered earlier, disclosure could take several minutes. When a typical outpatient visit takes less than 15

minutes, it becomes clear that the activity of financial disclosure may itself cause economic harm to the patient. This harm could be lessened by having personnel whose time is less expensive than a physician's—nurses, social workers, interactive videos—perform the task, but situations could still occur wherein a patient would receive $10 worth of disclosure and counseling regarding an $8 test.

Disclosure in the Balance

Who should decide whether the benefits of disclosure outweigh the harms and costs—the patient or the physician? Although this debate is unresolved, we offer some practical suggestions, realizing that discussions of cost will not be practical in every physician-patient encounter. First, in cases where a patient is unable to comprehend the information, disclosure should not be carried out. Second, in cases where there is reason to think that unsolicited information might be truly harmful, disclosure should be avoided or delayed. Third, when a patient asks for financial information, it should be provided, along with alternatives.

What are other options for financial disclosure? We have already mentioned nondisclosure, disclosure by physicians, disclosure by other health care professionals, disclosure by administrators, and disclosure using interactive media (such as interactive CD-ROM or computer). Another possibility is to develop practice guidelines that specifically incorporate patients' preference in the context of the net benefit-cost trade-offs. Consider a staff-model HMO. Rather than leaving the cost disclosure decision to the discretion of each physician, the plan might assemble a representative group of its members and present them with different points of view—the patients', physicians', administrators', and the like—regarding the benefits, harms, and costs of pregnancy tests in fertile women with abdominal pain. The assembled members would then decide on a baseline practice policy for the plan.

Such a model goes beyond standard clinical guidelines in that it asks plan members to consider not only what is medically desirable, but also what makes sense in terms of cost. This process would work best with problems for which there is general homogeneity of patient preference within the plan.

Of the choices we have outlined, we least prefer disclosure by administrators. Introducing a third party in the middle of the patient-physician relationship will only confuse the issue and may diminish the therapeutic bond between patient and physician. Passing the patient off to an anonymous "financial counselor" who knows little about the patient or the circumstances is undesirable regardless of the counselor's title or training. The choice among the remaining alternatives should be based on the cost of disclosure relative to the medical and economic importance of the decision.

In principle, we think that discussions about cost of care are an important part of the physician-patient relationship and that financial well-being is certainly within the boundaries of most peoples' concept of health. Only through careful discussions of these topics can a physician be a patient's best advocate. On occasion, the physician may disagree with the patient but can still assist by suggesting less costly alternatives, negotiating with insurers, or acting in an advocacy role as the patient works out the best course of action.

Interactive media presentations have been shown to be useful in helping patients choose among treatment alternatives and could certainly be adopted to handle questions of cost.[27] Such systems, while expensive to purchase, could provide most of the information that the patient needs, and the physician would only need to answer the patient's remaining questions.

Conclusion

We acknowledge that the absence of evidence demonstrating the value of financial disclosure and the myriad practical impediments to instituting routine disclosure preclude us from offering any firm recommendations on this topic. Nevertheless, it is time that practitioners and administrators begin to consider these issues so that health care at both the individual and societal level can be planned in more rational ways. Acknowledging our discomfort with the overt consideration of the relationship between cost and care for individual patients is the first step toward successfully dealing with our national health policy. If we cannot rationally approach the care of a single patient in the context of cost, how can we expect to do so for 200 million patients? Furthermore, by making patients more aware of cost, we may better inform the public of the realities of spiraling costs of health care. Only in this manner can members of society prepare to engage in the debate regarding which health care services should be provided by society and for whom. This type of patient education remains our best hope for increasing the likelihood that our government representatives will be able to design a logical, compassionate, and intelligent health care system. Over the past 30 years, we have empowered our patients by giving them information about the possible benefits and harms of treatment alternatives.[28] It is time we take the next step and provide people with information about cost. By doing so, we let them integrate health care decisions into the context of their lives and increase their capacity for individual and societal self-determination.

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Editorials

California's 1988-1991 Measles Epidemic—The Last One?

ELSEWHERE IN THIS ISSUE, Chavez and Ellis document the severe effects of California's 1988-1991 measles epidemic.[1] Several other investigations of this epidemic have chronicled its extraordinary toll.[2-6] The epidemic resulted in more than 18,000 reported cases, 3,500 hospital admissions, and 70 deaths. In large part, as Chavez and Ellis note, this was an epidemic among unimmunized, economically disadvantaged minority infants and young children. More than half of the patients were younger than 5 years, 84% were unimmunized, and at least half were Latino, African American, or Asian. The epidemic was not restricted to children, however; more than 4,000 adults were stricken.

As Chavez and Ellis aptly point out, the epidemic reminds us that measles can be a serious disease producing severe complications and lengthy, costly hospital stays. More than 10% of patients had diarrhea, many to the point of substantial hypovolemia. Pneumonia developed in nearly 10%, with some of these cases progressing to the adult respiratory distress syndrome (ARDS) and requiring prolonged ventilatory support. Most of the deaths resulted from this latter complication.

The high morbidity and mortality rates can be partially explained by the fact that more than 80% of the cases occurred in infants, toddlers, or adults—the ages at which measles infection is most severe—and by the extraordinary frequency of severe complications observed among Samoan and Hmong infants and young children. Further, a vivid demonstration of the danger posed by measles to medical staff is that in this epidemic more than 150 cases were reported among medical staff; 3 of these died, 1 was left paralyzed, and another recovered only after severe ARDS developed that required ventilatory support for several weeks.

The financial effects of the epidemic were substantial, with direct medical care and outbreak control costs alone estimated at $31 million.[2] Analyzing data on pediatric hospital admissions, Chavez and Ellis found that the average hospital stay was 4.6 days and the average hospital cost was $8,200. They also note that two thirds of this cost was incurred by Medi-Cal (California's Medicaid) beneficiaries. The brunt of the fiscal effects was borne directly by the taxpayers.

The key to preventing the recurrence of measles epidemics of this type is to raise the immunization coverage of preschool-aged children. Measles immunization is recommended for all children at 12 to 15 months of age. Unpublished surveys conducted by the California Department of Health Services, however, indicate that at the time of this epidemic, less than half of California children were immunized against measles on time. In fact, by age 24 months (almost a year older than the recommended age), only 70% had been immunized.

To explore further the causes of the epidemic, the California Department of Health Services conducted an ecologic study of relationships between demographic features and measles incidence rates among children younger than 5 years for the California counties affected by this epidemic.[6] Three independent predictors of high measles incidence by county were identified with the use of a stepwise multivariate regression analysis. The first of these was the percentage of county population younger than 5 years. This finding supports the obvious point that a large population of preschoolers with low immunization coverage increases the risk of measles outbreaks. The other two independent predictor variables of a high measles incidence were factors related to access to immunizations: a high number of poor children per government third-party-payer provider (that is, Child Health and Disability Prevention, or CHDP, and CHDP–Medi-Cal programs in California) and the high number of poor children per public health immunization site. This finding strongly suggests that a limited supply of primary and preventive health care professionals in relation to the number of poor children in a community increases the epidemic risk.

In the years since the epidemic, considerable resources have been committed in California and the rest of the United States to raise immunization levels among preschool-aged children. Both state and federal funds have been used to expand the availability of immunization services, particularly for children in low-income families. Efforts are under way to improve parental awareness and motivation regarding immunizations and to develop computerized immunization tracking systems that can remind parents and health care professionals that immunizations are due. Although changes in assessment methods make it difficult to quantify the increase in immunization levels with precision, the immunization coverage of preschoolers has improved substantially since the epidemic.[7]

There is still room for improvement, however. Public and private health care sectors and other segments of the community must continue coordinated efforts to ensure that more infants and young children, especially economically disadvantaged minority children, receive immunizations and other preventive health care services in a timely manner. Health care professionals should view every medical visit by an infant or preschool-aged child as a possible opportunity to assess immunization status and to administer immunizations. Several investigations have shown that if medical care professionals aggressively make use of such opportunities, they can substantially improve immunization coverage.[8,9]

Finally, the two-dose measles immunization schedule—given as combined measles-mumps-rubella, or MMR vaccine—recommended for all children by the United States Public Health Service Advisory Committee on Immunization Practices, the American Academy of Pediatrics, and the American Academy of Family Physicians deserves full implementation.[10] Whereas single-dose

measles immunization is as much as 95% effective,[11] a 5% vaccine failure rate is still too high for a disease as infectious as measles. Even with this low vaccine failure rate and with a well-enforced school-entry requirement, one-dose measles immunization has been inadequate to prevent school measles outbreaks among the remaining susceptible pupils.[12] The accumulation of susceptible persons in a population resulting from this vaccine failure rate has also been associated with recurrent community-wide measles outbreaks.[13] It should also be noted that during California's 1988-1991 measles epidemic, more than 3,500 cases occurred in school-aged children, almost half of whom had previously been immunized. In response to this problem, 40 other states have changed their school-entry measles immunization requirement from one to two doses. California should give serious consideration to doing the same.

If California is successful in immunizing at least 90% of its children against measles in their second year of life and in ensuring the receipt of a second dose of measles-containing vaccine by nearly all children through a school-entry immunization requirement, the devastating 1988-1991 measles epidemic could prove to be California's last one.

NATALIE J. SMITH, MD, MPH
LORING G. DALES, MD, MPH
STEPHEN H. WATERMAN, MD, MPH
Division of Communicable Disease Control
California Department of Health Services
Berkeley, California

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Progress in Treatments for Substance-Impaired Physicians

The publication of "Substance-Impaired Physicians—Probationary and Voluntary Treatment Programs Compared" by Nelson and colleagues in this issue of The Western Journal of Medicine highlights continuing progress in effective treatments for impaired physicians.[1] The comparison of probationary and voluntary groups in this study addresses critical public policy outcomes. These issues have been debated since changes in treatments for impaired physicians in the 1970s. The study focuses our attention on probationary treatment under a state board of medical examiners and compares it with voluntary treatment under an independent state physician health program. It assists us in refocusing on the important debate concerning protection of the public through coerced probationary treatment versus voluntary treatment that can occur at an earlier stage of intervention. We should pay close attention to the lessons here because they may guide us to more effective interventions that can save the health and careers of hundreds of physicians while safeguarding the public.

Since the 1970s, there has been considerable progress in developing and evaluating interventions for impaired physicians. Leadership has come from the American Medical Association, some state medical boards, and professional societies. In the West, model programs have been developed in Oregon, Washington, California, Arizona, and Colorado. The treatment method of contingency contracting is widely accepted. This method involves a patient consent agreement that links monitored drug abstinence to continued medical licensure. Another critical issue is a comprehensive assessment of impaired physicians to identify all comorbid medical and psychiatric disorders. Unfortunately, this goal is not accomplished in all programs; the tension between "addiction" and "psychiatric" treatments continues to inhibit comprehensive assessment and care in some treatment settings. To treat an addictive disorder without dealing with other possible complicating psychiatric conditions—for example, major depression—is short-sighted and ineffective. Despite these problems, treatment effectiveness for impaired physicians as reported in the outcome research is outstanding. It is 80% or above in several studies. Whereas special groups such as airline pilots and physicians cannot be compared with other patient groups because of the intensity of their monitored supervision, the success of some state board programs in combination with voluntary physician health programs provides stellar examples of both public accountability and humane treatment with vocational rehabilitation.

The Nelson study compared characteristics and treatment outcomes of substance-impaired physicians in Oregon. This is a retrospective, nonrandomized, clinical method comparing the cases of 97 physicians who were treated either in the state board probationary program or in a voluntary diversion program. Results were positive for both groups. The study identified a cohort effect with the voluntary diversion group, including a younger group

and more trainees, suggesting earlier intervention. There was evidence, however, that the board probationary group had a more complicated prognosis, perhaps contributing to their probationary status in the first place. The authors also provide a valuable reference by summarizing and comparing results from 12 impaired physician programs from around the country.

The Oregon study should reassure state medical boards that collaboration with voluntary physician health programs may identify impaired physicians at an earlier stage of intervention and prevent progression of the addictive or psychiatric disorder. Because this retrospective method is typical of impaired physician program research, however, the study also calls attention to current limitations in treatment outcome research in this subspecialty area. Such studies cannot definitively address many important questions, such as exact comparison of risk factors and policy questions concerning public protection versus rehabilitation. The field needs to review seriously and advocate for research studies with methods that move beyond retrospective comparisons of medical records to prospective studies with carefully matched samples. In addition, this study and others have shown substantially positive results from the partnerships between some state medical boards and their corresponding voluntary physicians health programs that identify impaired physicians early and divert them away from a probationary licensure status. The high variation of these studies among states highlights the national inconsistency in our approach to impaired physicians. In my opinion, this inconsistency becomes an indefensible position for both public policy and rehabilitation. At this time, we need a definitive national survey that evaluates the status of probationary and voluntary programs on a state-by-state basis with the goal of standardizing the referral-assessment-treatment approaches. Our outcome data are now sufficiently comprehensive to support a national initiative that both protects the public and saves additional physician lives and careers.

JAMES H. SHORE, MD
Professor and Chair
Department of Psychiatry
Superintendent
Colorado Psychiatric Hospital
University of Colorado Health Sciences Center
Denver

REFERENCE

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Correspondence

Genetics and Homosexuality

To the Editor: I was appalled and offended by the implication that male homosexuality is a "psychiatric" or "behavioral disorder," genetically linked, in this classification, with "human aggression," "anxiety or neuroticism," "attention-deficit hyperactivity and reading disability," "novelty seeking," "schizophrenia," and "manic depressive illness," as discussed by Reus in the March 1996 issue of The Western Journal of Medicine.[1] Genetic linking of sexuality or sexual preferences is as normal as genetic linking of gender, skin color, and many other human attributes and should not be listed in a grouping of otherwise abnormal behaviors or illnesses.

LINDA H. MORSE, MD
Chief, Occupational Medicine
Kaiser Permanente Medical Center
601 Van Ness Ave #2008
San Francisco, CA 94102

REFERENCE

1. Reus VI: Behavioral genetics. West J Med 1996; 164:260

* * *

Dr Reus Responds

To the Editor: Linda H. Morse, MD, is mistaken in her interpretation of my comments in the epitome in the March 1996 issue of The Western Journal of Medicine. There was no intended nor actual linkage of male homosexuality to psychiatric or behavioral disorders. The review was of a number of recent studies in "behavioral genetics," and while it is true that many have focused on specific illnesses, several have attempted to find genetic determinants of normal complex human traits. The epitome, which was critical of premature interpretations in this area, included two studies that explored normal behavior, one investigating the temperament dimension of "novelty seeking," and the other, male homosexuality. It should be pointed out that the study associating the dopamine D_4 receptor polymorphism with the personality trait of "novelty seeking," reported by Ebstein and co-workers, used normal volunteers from a hospital and university in Israel and that their findings were replicated by a group from the National Institutes of Health on a cohort of 315 normal subjects who were evenly split with regard to homosexual or heterosexual orientation.[1]

The recent finding on homosexuality does not exclude the possibility of genetic contributions to heterosexuality, and such reports would have been included had they been available; the imputation of abnormality would be inappropriate in either case, as it would reflect a social judgment rather than a biologic fact. The study of homosexuality by Hamer and colleagues was published in a leading journal, received widespread media attention, and has been expanded into a book for the lay public.[2] I do not agree with Dr Morse that it should not be discussed along with other studies of the genetics of behavior, any more than I feel that a finding of a gene for skin color or hair growth should be prohibited from being mentioned in a review of genetic findings in dermatology or a gene for nutritional preference in a discussion of genetic advances in cardiology.

VICTOR I. REUS, MD
Professor
Department of Psychiatry and Langley Porter Institute
401 Parnassus Ave, Box F-0984
San Francisco, CA 94143-0984

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The Editors are pleased to receive letters commenting on articles published in the journal in the past six months, as well as information or short case reports of interest to our readers. ALL MATERIAL SUBMITTED FOR CONSIDERATION MUST BE DOUBLE-SPACED. Letters NO LONGER THAN 500 WORDS are preferred. An original typescript and one copy should be submitted. All letters are published at the discretion of the Editors and subject to appropriate editing. Those of a scientific nature will be peer reviewed. Authors should include information regarding conflict of interest, when appropriate ("I warrant that I have no financial interest in the drugs, devices, or procedures described in this letter"). Most letters regarding a previously published article will be sent to the authors of the article for comment. Authors of accepted letters will have an opportunity to review the edited version before publication.

Lessons From the Practice

Mrs O'Brien's Story

GARY S. REITER, MD, *Holyoke, Massachusetts*

Mrs O'Brien was a new patient to the practice when she was squeezed into my schedule on an overbooked day. She had severe back pain. The patient was standing when I entered the examination room. She looked at me expectantly, in obvious discomfort. Taking a seat, I asked Mrs O'Brien to tell me about her back pain.

She began. While she and her husband, Jack, were vacationing on Cape Cod last summer, he had a major heart attack and died three weeks later. The details poured out: the hospital on Cape Cod; the kind and caring emergency physician they had seen there; where the doctor had gone to college, medical school, trained, and even grown up. She told me about Jack's emergency transport to the biggest hospital in Boston, the names, backgrounds, and qualifications of the interns and residents who cared for him there, and what it was like to wait with him through endless rounds of specialists, subspecialists, laboratory tests, and procedures.

By the time I interrupted her and began a more directed history of her back pain, Mrs O'Brien had worked her way through only the first week of Jack's final illness. Yet, it seemed like she had told me the names and personal histories of all his caregivers, as well as those of her children and grandchildren. I examined the patient and asked some specific questions about her back pain. I told her she probably had sciatica and prescribed some analgesics and a course of physical therapy. She made an appointment to see me in two weeks.

Two weeks later, when I entered the room to see Mrs O'Brien, she again was standing. She said that her back pain was no better. She hadn't taken the analgesics and hadn't gone to physical therapy. When I asked her what had happened, she began again with the story on Cape Cod, her husband, and his heart attack. This time, I let her tell me the whole story.

It was difficult to sit through the entire 40-minute story, but I did. At the end, I thanked her for telling me about Jack. The story of his death and her grief were still an important part of her. Amazingly, she hadn't shared her grief with anyone else. Nor had she found a spiritual outlet for her grief. Although she attended church regularly, she had never said any special prayers for her husband or acknowledged his death in any spiritual way.

I told her how in my religion, Judaism, we formally mourn for a year. At the end of the year, we have a special ceremony to commemorate the death of the loved one. That commemoration also marks the time for us to cease grieving and to fully return to our lives, although on the anniversary of their deaths and on special holidays, we continue to remember those who have died. I suggested that she pray for her husband at church and that she do something during the summer to mark the end of a year of mourning. I also reexamined her and made an appointment for her to go to physical therapy.

Mrs O'Brien was sitting in a chair, reading a magazine, when I entered the room to see her for her follow-up visit. She said that her back had improved greatly. She couldn't say enough about how wonderful the staff was at the physical therapy clinic. She thanked me for taking the time to speak with her about her husband. She said she had begun to pray for her husband and had decided to mark the anniversary of his death by bringing her family together at their summer home on Cape Cod.

I have seen Mrs O'Brien several more times. Her back pain doesn't bother her much anymore. Although we have not talked again about the events on Cape Cod, I know now that I couldn't really be Mrs O'Brien's doctor until she had told me that story.

(Reiter GS: Mrs O'Brien's story. West J Med 1996; 165:84)

Dr Reiter is in private practice in Holyoke, Massachusetts.
Reprint requests to Gary S. Reiter, MD, 15 Hospital Dr, Ste 403, Holyoke, MA 01040.

Gloria! . . . Glooooria!

ELLIOTT B. OPPENHEIM, MD, JD, LLM *Grosse Pointe, Michigan*

We had 12 Christmases together. Every year around Christmas, she came to see me for her yearly visit. We would chat, and I'd hear about her husband and her little boy. Every time I'd see her, I noticed her inner strength and calm. Then we'd say our good-byes, and I would see her again only when her boy got a cold or when she had some minor ailment.

A few years after we met, her husband left her. During her divorce, she suffered greatly. He wanted to take the boy and move a long way away. We talked a long time at that visit, and she clutched her chart while we talked. When she left, there was a wet handprint on it and some teardrops that smudged my jottings from another visit. About a week later, her husband violated a restraining order, picked their boy up after school, and sped away. He was drunk and on drugs, and at an intersection he went through the stop sign. A large delivery truck, which had the right of way, swung wide but was unable to avoid hitting the car. Both the husband and son died.

I saw Gloria in the middle of the night in the emergency department. She called me, her only doctor, not wanting to see anyone else. She was wrung out. How can anyone cope with such a loss? She was vomiting up her grief. Why had this happened to her? I was honest and told her that I had no special insight into why these things happened. She accepted that. After some talk and some medicine, she took a few days off to rest and then went back to work. She invited me to the funerals, but I have a policy. I will attend only one funeral: mine. I wanted to go for her sake, but I couldn't.

When I next saw her, it was around Christmas again. She smiled, and I could see that she had done the short-term repair work. She was seeing a guy. "I've known you a long time now," she observed. "What's it been? Six years? I have nobody anymore. My parents died when I was young, and now I'm all alone. I count on you," she confided. I was honored.

I told her she could come see me any time, and I meant it. Gloria was a good person, and I wanted to help her in any way I could. A couple more years slipped by. When Gloria came for her next visit, she brought me a basket of pineapples and some chocolate macadamia nut fudge from Kauai, Hawaii. She had met another guy. He was kind and sweet and had a good job. They had spent ten days together in Hawaii. She showed me a few photographs. She seemed to glow like the sunset.

"My new guy? His name is Milton. He's really smart and sells artist supplies. He's a painter, too." Then she unwrapped a painting. "It's called 'Kissing Fishes,' but it's us! Could you tell?" I hadn't heard giggles like that from her in years. It was a grand Christmas that year.

Another year passed and then another. Then she came in, looking worried. "I have a lump," she told me.

"How long?"

"It came in July."

"Why did you wait until December to come see me?" I was mad, but held back.

"I don't know. I just hoped it would go away. Heck, with what's happened to me, there couldn't be any more bad, could there?"

I sank an 18-gauge needle into the center of the lump located in the upper outer quadrant of her left breast. As the needle went in, there was a gritty crunching, and I already knew the diagnosis. I think she did, too. The biopsy showed an undifferentiated cancer, and I sent her over to my surgeon. He took out the lump, but all of her lymph nodes were positive.

After half a year of irradiation, chemotherapy, and hoping, she had a disease-free interval of about 15 months. When she returned, I didn't need a complete blood count and SMA panel to tell me what was obvious. She was deeply jaundiced and could barely breathe. And she was tired of her medical ordeal. She couldn't tolerate any more IVs, and we talked for a long time. Her oncologist was an academic sort, and she couldn't talk much to him, so we talked about twice a week. Gloria was dying, drowning in her pulmonary secretions.

Milton painted all day long as she watched him, and I visited her every day. I scheduled my life around her life and took my kids to visit her. The kids took her illness hard because they remembered her as chunky and jovial and strong. They had grown up with Gloria, and she had grown up with them. Laura baked cookies with lots of nutrients and made Gloria milkshakes with almond flavoring. But Gloria continued to lose pounds and breath. She was tachypneic at rest and refused to let me do a chest x-ray. "I don't want to know anything. I just want to die," she said.

"Maybe you have an effusion. I can take it off with a needle, and you'll breathe better," I argued, but she tried to joke between gasps.

"An . . . eff . . . usion, huh? How could I . . . have any . . . thing more go wrong?"

(Oppenheim EB: Gloria!. . . Glooooria! West J Med 1996; 165:85-86)

From CoMEDco, Inc, a Washington Corporation. Dr Oppenheim practiced family medicine before becoming a medical-legal consultant.
Reprint requests to Elliott B. Oppenheim, MD, JD, LLM, 8110 146th Ct NE #25, Redmond, WA 98052.

I took off about a liter of fluid from both sides. She felt wonderful for about three weeks, but then she told me, "Look, I've had it. Do . . . you . . . get it?"

I gave her Nembutal [pentobarbital sodium] suppositories and morphine but told her that I couldn't do what she wanted. I instructed her in how to relieve her pain. She and Milton would take it from there, she gasped to me.

I sobbed all the way home, thinking she was gone. I couldn't stand the loss. But the next morning I got a call from Milton. "She's gonna stick this out. She says she can't leave at this time of the year. Weather's too good. She could use some magic, though. Got any more of those cookies?"

I invited a magician friend to go to her home with me and my kids and my office nurses, and with Milton, we celebrated her birthday with a real magic show. Her birthday wouldn't be for another six months, but she wanted a party, so we gave her one. She laughed quietly and enjoyed the 30-minute respite from reality.

She lasted only a few more days. All of us went to her funeral. I had never seen my kids so upset. They spread her ashes in the Puget Sound. I closed the office for three days. I couldn't get out of bed.

Five years later, I still miss Gloria. Every time I hear the Christmas carol, I think of her and what a person she was. She enriched us so by her dignity and strength, by her ability to smile and to manage to find humor in unfunny things so as to cheer us up. When I hear that carol, it's as if she's calling me from heaven, showering me with her love and strength.

I hope I was a good doctor for her. I held her chart on my chest while I thought about all this and rocked in my chair. I did all that I could, but her dying left me with a question I still can't answer. She died at 34. Why do things like that happen? I put her chart into the deceased file and notice another wet handprint on it and new wet smudges where I'd written, "Gloria! Glooooria!"

* * *

Lessons From the Practice

Courage

ANONYMOUS

She is 27 years old and has had systemic lupus erythematosus for 12 years. She has suffered through pneumonitis, pericarditis, cerebritis, hepatitis, thrombocytopenia, and osteonecrosis of the hips and knees. She has had a knee replacement, plasmapheresis, a splenectomy, and surgical debridement of large soft tissue abscesses. She would always say that she was lucky because her kidney function was good. The only thing she wanted was a baby—she knew the risks, but was willing to take them.

She couldn't do many things, but she loved life; her smile lit up the world of those around her. With the enormous medical bills, her husband couldn't buy her many of the things she desired. But she still loved to shop for shoes, clothes, and jewelry. Her appearance was important to her. Despite the ravages of her disease, she took pride in the parts of her body that were beautiful and untouched—her hands, face, and breasts. She cared for her skin meticulously with moisturizers and lotions. She had beautiful, delicate hands and enjoyed having her nails manicured and polished.

In May, her feet became swollen. Her desire to buy fancy shoes went away. Her gratitude for good kidneys was lost, as tests confirmed membranous glomerulonephropathy. The risk of pregnancy became insurmountable. But she moved on with her life.

In July, anasarca developed. The joy of buying new clothes went away as she went from size 4 to size 10. She would look in the mirror and cry. But she adjusted and went on with her life. In October, the distal third of the left index finger became necrotic and, later, had to be amputated. The joy went out of buying rings and jewelry; she no longer had her nails manicured and polished. Everyone said that it was no big deal—that it was the left hand, anyway. That didn't stop her tears. But she adjusted and went on with her life.

The nephrotic syndrome and diuretics caused large fluid shifts. These, in combination with high doses of steroids, caused the development of striae. Her beautiful breasts became edematous and marred with striae, and her abdomen became a map. Still, she did not give in to despair—she went on with her life.

Today she, my wife, had a wide smile as she returned from Nordstrom. "Honey," she said, "look at my two new handbags."

She goes on with her life.

(Anonymous: Courage. West J Med 1996; 165:86)

No reprints are available.

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Our readership represents all specialties of medicine. We wish to receive and publish manuscripts that are valid, important, lively, well-written, and succinct. They should be of interest to a broad range of busy practitioners, students, researchers, and scholars who have a clinical orientation. The purpose of a paper or letter may be to alert, review, discuss—above all, to teach. Titles should be short and intriguing. Avoid jargon, the overuse of abbreviations and acronyms, sexist language, redundancies, or expendable words and phrases (see *AMA Manual of Style,* 8th Edition).

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Journal Articles

Abbreviations of journal titles should conform to those used in *Index Medicus*. List up to six authors; for seven or more, use et al after listing the first three.

1. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

2. Jones JS, Anderson HW Jr, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

Books

3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press 1966, pp 35-51 [author of book is same as author of chapter]

4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Edition. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 [authors of book differ from chapter author]

Correspondence

5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

Government Publications

6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983

7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intraarterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

Mass Circulation Publications **(Do not include in reference list; put in text)**

(T. Harris, "Selenium-Rich Sediments Also Have Been Reported in Wildlife Refuges," *The Sacramento Bee*, September 8, 1985, p 5)

Personal Communications and Unpublished Data

This material should not be included in the reference list but should be given in parentheses in the body of the text, listing the person's name, highest academic degrees, and professional affiliation, whether the communication was oral or written, and the date (month and year).

Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

(Continued from Page 13)

September 20—**Ophthalmology: Clinical Faculty Day**. Fri. 7 hrs. $65. Contact: UUSM.

October 4-5—**Western Intermountain Neurological**. University Park Hotel, Salt Lake City. Fri-Sat. 12 hrs. $75. Contact: UUSM.

October 7-9—**Preconference Workshop**. Mon-Wed. $500. Limited to 15. Contact: UUSM.

October 10-13—**Intensive Interactive Head and Neck Imaging**. University Park Hotel, Salt Lake City. Thurs-Sun. 30 hrs. $750. Contact: UUSM.

December 6-12—**Intensive MR Imaging and Neuroradiology**. Marriott Hotel, Salt Lake City. Fri-Thurs. 30 hrs. $1,250. Contact: UUSM.

February 5-9—**3rd Annual Brigham & Women's Utah Therapeutic GI Endoscopy Course 1996: Problems and Solutions**. Park City. Contact: UUSM.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

SPONSORS OF COURSES—ABBREVIATIONS

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ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS:	Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

September 5-7—**Impact of Bacterial Antibiotic Resistance on Oral Health: What is the Relevance?** Seattle. Thurs-Sat. Contact: U/W Dept of Environmental Health, (206) 543-1069.

September 6-7—**Collaborative Practice.** Seattle. Fri-Sat. Contact: U/W.

September 6-7—**Radiation Risk Communication**. Seattle. Fri-Sat. Contact: U/W Dept of Environmental Health, (206) 543-1069.

September 9-13—**24th Annual Advances in Family Practice**. Seattle. Mon-Fri. Contact: U/W.

September 18—**Random Acts in Geriatrics**. Seattle. Wed. Contact: Providence/Seattle Medical Center, (206) 320-2552.

September 19—**Diagnosis and Treatment of Peripheral Vascular Disease**. Everett. Thurs. Contact: Providence General Medical Center, (206) 261-3690.

September 20—**Cardiovascular Risk Factors**. Seattle. Fri. Contact: Virginia Mason, (206) 223-6898.

September 20-22—**Pacific NW Diagnostic Ultrasound.** Seattle. Fri-Sun. Contact: Swedish Medical Center, (206) 386-2265.

September 24—**Low-Molecular-Weight Heparin**. Seattle. Tues. Contact: Swedish Medical Center, (206) 386-2265.

September 24—**Washington's Children Health Policy Conference.** Seattle. Tues. Contact: Children's Continuing Medical Education, (206) 526-2501.

September 25—**MHTRP—Fall Conference**. Seattle. Wed. Contact: Children's Continuing Medical Education, (206) 526-2501.

September 25-27—**Evaluation of Permanent Impairment**. Yakima and Everett. Wed-Fri. Contact: U/W Dept of Environmental Health, (206) 543-1069.

September 26-28—**Surgery Update—Harkins Society Annual Straus Lecture.** Seattle. Thurs-Sat. Contact: U/W.

September 27-28—**ACLS**. Seattle. Fri-Sat. Contact: Swedish Medical Center, (206) 386-2265.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

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July 22-25, 1996

5th Annual General Surgery Update
The Cloister, Sea Island, GA
July 26-28, 1996

4th Annual Primary Care Update: What's New in Dermatology
Kiawah Island Resort, Kiawah Island, SC
July 26-28, 1996

Sports Medicine & Soccer Symposium
The Parliament House, Birmingham, AL
July 26-28, 1996

Advanced Orthopaedic Imaging
The Cloister, Sea Island, GA
July 29-August 1, 1996

Pain Management in the Office Setting
The Cloister, Sea Island, GA
August 2-4, 1996

Advances in Geriatric Medicine
Lago Mar Resort & Club, Ft. Lauderdale, FL
August 9-11, 1996

Gastroenterology Update for Primary Care
Marriott's Bay Point Resort, Panama City, FL
August 16-18, 1996

Common Clinical & Practice Skills: Use & Interpretation
Ritz-Carlton-Palm Beach, Manalapan, FL
August 23-25, 1996

Inaugural Conference on Managed Care
Swissotel, Atlanta, GA
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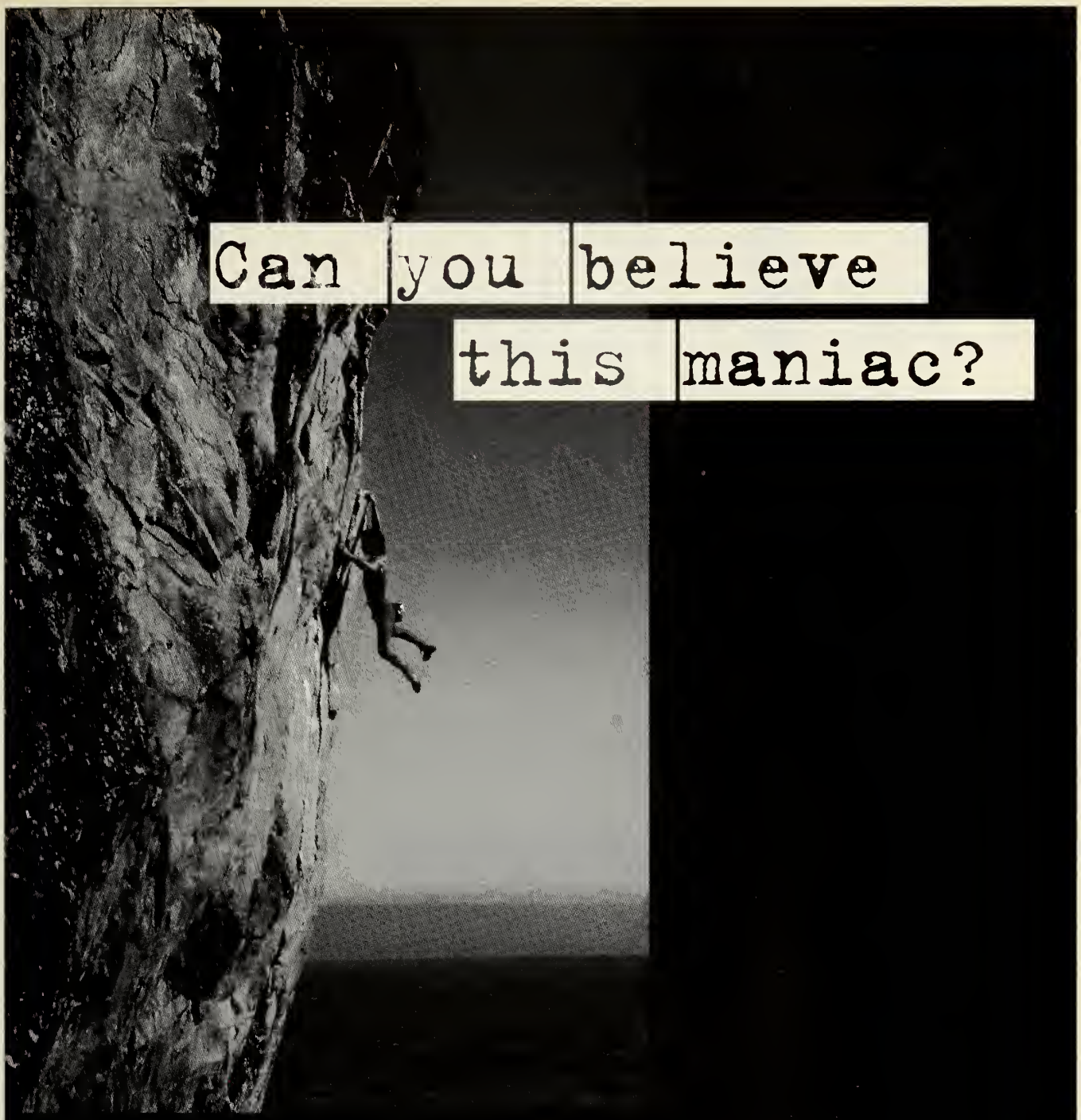

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AAD 91

NATIONAL ARBOR DAY FOUNDATION 1

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The Western Journal of Medicine

VOLUME 165 • NUMBER 3 SEPTEMBER 1996

ARTICLES

112 Torture and War Trauma Survivors in Primary Care Practice
HM WEINSTEIN, L DANSKY, and V IACOPINO

119 Trends in California Homicide, 1970 to 1993
LD CHU and SB SORENSON

126 Epidemic *Salmonella enteritidis* Infection in Los Angeles County, California—The Predominance of Phage Type 4
DJ PASSARO, R REPORTER, L MASCOLA, L KILMAN, GB MALCOLM, H ROLKA, SB WERNER, and DJ VUGIA

CONFERENCES AND REVIEWS

131 Predictors of Thyroid Tumor Aggressiveness
OH CLARK

EPITOMES

139 Important Advances in Occupational Medicine

ALERTS, NOTICES, AND CASE REPORTS

144 Propylthiouracil-Induced Hepatotoxicity
JT HARDEE, AL BARNETT, A THANNOUN, B EGHTESAD, M JAMAL and D WHEELER

147 Venlafaxine Hydrochloride and Chronic Pain
K TAYLOR and MC ROWBOTHAM

TOPICS IN PRIMARY CARE MEDICINE

149 Action Plans in Asthma Management—Why, When, and How?
S JANSON

COMMENTARY

154 Broken Promise
LJ PURDY

EDITORIALS

156 Prognostic Factors and Management in Thyroid Cancer—Consensus or Controversy?
SKG GREBE and ID HAY

157 Asthma Management—A Call for Action
RE DALES

159 The Order of the Day? Cheers, Thanks, and Introductions
LH CLEVER

CORRESPONDENCE

161 Female Prostatitis? • Jarisch-Herxheimer Reaction

LESSONS FROM THE PRACTICE

163 The Extra Window
L MONTAUK

164 Selective Deafness
S AUSTER

OTHER FEATURES

103 Subscription Information

106 Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming

165 In Memoriam

166 Instructions for Authors

168 Business and Subscription Information

170 Classified Advertising

176 Western State Medical Associations' Meetings

Detailed Table of Contents: 100, 102, 104

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Please see brief summary of prescribing information for contraindications, warnings, precautions, adverse reactions, and dosage and administration on adjacent page.

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References: 1. Neu HC, Wilson APR, Grüneberg RN. Amoxycillin/clavulanic acid: a review of its efficacy in over 38,500 patients from 1979 to 1992. *J Chemother* 1993;5:67-93. **2.** *Clinical Efficacy Updates I-IV,* 1996, SmithKline Beecham Pharmaceuticals.

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Lower Respiratory Tract Infections caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis* *Otitis Media* caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis* *Sinusitis* caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis* *Skin and Skin Structure Infections* caused by β-lactamase-producing strains of *Staphylococcus aureus, Escherichia coli,* and *Klebsiella* spp *Urinary Tract Infections* caused by β-lactamase-producing strains of *E coli, Klebsiella* spp and *Enterobacter* spp While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content Therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic Because amoxicillin has greater *in vitro* activity against *Streptococcus pneumoniae* than does ampicillin or penicillin, the majority of *S pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin and *Augmentin* (See Microbiology subsection)
Bacteriological studies to determine the causative organisms and their susceptibility to *Augmentin* should be performed together with any indicated surgical procedures Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above Once results are known, adjust therapy, if appropriate
CONTRAINDICATIONS: Patients with a history of allergic reactions to any penicillin, or patients with a history of *Augmentin*-associated cholestatic jaundice/hepatic dysfunction
WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS BEFORE INITIATING THERAPY WITH *AUGMENTIN*, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.** Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic associated colitis " After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis Use *Augmentin* cautiously in patients with evidence of hepatic dysfunction Hepatic toxicity associated with *Augmentin* use is usually reversible On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide) These have generally been cases associated with serious underlying diseases or concomitant medications (See CONTRAINDICATIONS and ADVERSE REACTIONS)
PRECAUTIONS: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy
A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted
Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin Co-administration of probenecid cannot be recommended The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients There are no data with *Augmentin* and allopurinol administered concurrently
Drug/Laboratory Test Interactions: Oral administration of *Augmentin* will result in high urine concentrations of amoxicillin High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's Solution or Fehling's Solution Since this effect may also occur with amoxicillin and therefore *Augmentin*, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Tes-Tape®) be used
Following administration of ampicillin to pregnant women a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone and estradiol has been noted This effect may also occur with amoxicillin and therefore *Augmentin*
Carcinogenesis, Mutegenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential **Mutagenesis:** The mutagenic potential of *Augmentin* was investigated *in vitro* with an Ames test, a human lymphocyte cytogenetic assay, a yeast test and a mouse lymphoma forward mutation assay, and *in vivo* with mouse micronucleus tests and a dominant lethal test All were negative apart from the *in vitro* mouse lymphoma assay where weak activity was found at very high, cytotoxic concentrations
Impairment of Fertility: *Augmentin* at oral doses of up to 1200 mg/kg/day (5 7 times the maximum human dose, 1480 mg/m²/day, based on body surface area) was found to have no effect on fertility and reproductive performance in rats fed with a 2 1 ratio formulation of amoxicillin clavulanate
Pregnancy: Pregnancy (Category B): Reproduction studies performed in pregnant rats and mice given *Augmentin* at oral dosages up to 1200 mg/kg/day, equivalent to 7200 and 4080 mg/m²/day, respectively (4 9 and 2 8 times the maximum human oral dose based on body surface area), revealed no evidence of harm to the fetus due to *Augmentin* There are, however, no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed
Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary
Nursing Mothers: Ampicillin class antibiotics are excreted in the milk, therefore, caution should be exercised when *Augmentin* is administered to a nursing woman
ADVERSE REACTIONS: *Augmentin* is generally well tolerated The majority of side effects observed in clinical trials were mild and transient, <3% of patients discontinued therapy because of drug-related side effects The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%) The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose Other less frequently reported reactions include abdominal discomfort, flatulence and headache
The following adverse reactions have been reported for ampicillin class antibiotics
Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis, mucocutaneous candidiasis and pseudomembranous colitis Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (See WARNINGS) Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions urticaria or skin rash accompanied by arthritis, arthralgia, myalgia and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome) and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis) These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See WARNINGS.) A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin* The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued The hepatic dysfunction, which may be severe, is usually reversible On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide) These have generally been cases associated with serious underlying diseases or concomitant medications Interstitial nephritis and hematuria have been reported rarely Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin* Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely
DOSAGE AND ADMINISTRATION
Since both the *Augmentin* 250 mg and 500 mg tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), 2 *Augmentin* 250 mg tablets are not equivalent to 1 *Augmentin* 500 mg tablet. Therefore, 2 *Augmentin* 250 mg tablets should not be substituted for 1 *Augmentin* 500 mg tablet.
Dosage:
Adults: The usual adult dose is 1 *Augmentin* 500 mg tablet every 12 hours or 1 *Augmentin* 250 mg tablet every 8 hours for more severe infections and infections of the respiratory tract, the dose should be 1 *Augmentin* 875 mg tablet every 12 hours or 1 *Augmentin* 500 mg tablet every 8 hours
Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe Severely impaired patients with a glomerular filtration rate of <30 mL/minute should not receive the 875 mg tablet Patients with a glomerular filtration rate of 10 to 30 mL/minute should receive 500 mg or 250 mg every 12 hours, depending on the severity of the infection Patients with a less than 10 mL/minute glomerular filtration rate should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection
Hemodialysis patients should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection They should receive an additional dose both during and at the end of dialysis
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals (See WARNINGS)
Pediatric Patients: Pediatric patients weighing 40 kg or more should be dosed according to the adult recommendations.
Due to the different amoxicillin to clavulanic acid ratios in the *Augmentin* 250 mg tablet (250/125) versus the *Augmentin* 250 mg chewable tablet (250/62.5), the *Augmentin* 250 mg tablet should not be used until the pediatric patient weighs at least 40 kg or more.
Administration: *Augmentin* may be taken without regard to meals, however, absorption of clavulanate potassium is enhanced when *Augmentin* is administered at the start of a meal To minimize the potential for gastrointestinal intolerance, *Augmentin* should be taken at the start of a meal
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The Western Journal of Medicine, which first appeared in 1897 as the *California State Journal of Medicine*, is one of the world's most respected peer-reviewed journals. For nearly 100 years *WJM* has provided practical information on clinical medicine, ethics, health, and public policy to physicians.

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The California Medical Association is a voluntary, non profit association of 34,000 physicians. Faced with rising postage and printing costs and a drop in revenue, CMA sought a relationship with an outside publisher. "Achieving financial stability will give us the opportunity to develop and improve the journal's fundamental mission to apply science to the bedside and provide physicians with the most current practice and policy information," says *WJM* editor Linda Hawes Clever, MD With this focus, Dr Clever noted plans for a landmark issue in 1997, in cooperation with the Milbank Memorial Fund, exploring the effects of managed care on physicians, patients, and the public.

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VOLUME 165 • NUMBER 3 • SEPTEMBER 1996

CONTENTS

ARTICLES

112 **Torture and War Trauma Survivors in Primary Care Practice**

HARVEY M. WEINSTEIN, MD, MPH; LAURA DANSKY, PhD; and VINCENT IACOPINO, MD PhD

From the Survivors International and the Western Regional Office of the Physicians for Human Rights, San Francisco, California.

119 **Trends in California Homicide, 1970 to 1993**

LAWRENCE D. CHU, MS, and SUSAN B. SORENSON, PhD

From the School of Public Health, University of California, Los Angeles.

126 **Epidemic *Salmonella enteritidis* Infection in Los Angeles County, California—The Predominance of Phage Type 4**

DOUGLAS J. PASSARO, MD; ROSHAN REPORTER, MD; LAURENE MASCOLA, MD; LIGA KILMAN, BSc; GEORGE B. MALCOLM, BSc; HENRY ROLKA, BSc; S. BENSON WERNER, MD; and DUC J. VUGIA, MD, MPH

From the California Department of Health Services, Berkeley; the Los Angeles County Department of Health Services, Los Angeles, California; and the Centers for Disease Control and Prevention, Atlanta, Georgia.

CONFERENCES AND REVIEWS

131 **Predictors of Thyroid Tumor Aggressiveness**

ORLO H. CLARK, MD

From the Department of Surgery, University of California, San Francisco, School of Medicine and Mount Zion Medical Center, San Francisco.

EPITOMES—IMPORTANT ADVANCES IN OCCUPATIONAL MEDICINE

Occupational Medicine

Items of progress in occupational medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

139 **Preventing Workers' Hepatitis A, B, C, D, E, and G**

BRUCE N. LEISTIKOW, MD, MS

139 **Long-Term Effects of Air Pollution**

DAVID BERGLUND, MD, and DAVID ABBEY, PhD

140 **Use of Nucleic Acid in the Diagnosis and Management of Tuberculosis Amplification Tests**

JODY MEADOR, MD; DOUGLAS MOORE, PhD; and PENNY WEISMULLER, DrPH

141 **Latex Allergy**

DENNIS SHUSTERMAN, MD, MPH

142 **Decreasing Work Disability From Asthma**

PHIL HARBER, MD

(Continued on Page 102)

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AMAState-5/96

(Continued from Page 100)

ALERTS, NOTICES, AND CASE REPORTS

144 **Propylthiouracil-Induced Hepatotoxicity**

JAMES T. HARDEE, MD; ANGELA L. BARNETT, MD; ABDUL THANNOUN, MD; BIJAN EGHTESAD, MD; DONALD WHEELER, MD; and MAZEN JAMAL, MD

From the Department of Internal Medicine, Division of Gastroenterology; the Department of Surgery, Division of Liver Transplantation; and the Department of Pathology, University of New Mexico School of Medicine, Albuquerque.

147 **Venlafaxine Hydrochloride and Chronic Pain**

KIRK TAYLOR, MD, and MICHAEL C. ROWBOTHAM, MD

From the Pain Management Center, the Departments of Neurology and Anesthesia, University of California, San Francisco, School of Medicine.

TOPICS IN PRIMARY CARE MEDICINE

149 **Action Plans in Asthma Management—Why, When, and How?**

SUSAN JANSON, DNSc, RN

From the Department of Community Health Systems, University of California, San Francisco, School of Nursing.

COMMENTARY

154 **Broken Promise**

LAURENCE J. PURDY, MD

From the Clinical Laboratory Medical Group, Pomona Valley Hospital Medical Center, Pomona, California.

EDITORIALS

156 **Prognostic Factors and Management in Thyroid Cancer—Consensus or Controversy?**

STEFAN K.G. GREBE, MD, and IAN D. HAY, MB, PhD, FRCP

Division of Endocrinology and Internal Medicine, Mayo Clinic, Rochester, Minnesota.

157 **Asthma Management—A Call for Action**

ROBERT E. DALES, MD, MSc

From the Department of Medicine and Epidemiology and Community Health, University of Ottowa Faculty of Medicine, Ottowa, Ontario, Canada.

159 **The Order of the Day? Cheers, Thanks, and Introductions**

LINDA HAWES CLEVER, MD

(Continued on Page 104)

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WJM996

(Continued from Page 102)

CORRESPONDENCE

161 **Female Prostatitis?**

NORMAN E. PETERSON, MD

M. FRANCIS RUSSI, MD

161 **Jarisch-Herxheimer Reaction**

MARK A. MARINELLA, MD

LESSONS FROM THE PRACTICE

163 **The Extra Window**

LANCE MONTAUK, MD

From the University of California, San Francisco, Division of Emergency Medicine. Dr Montauk is an Attending Physician at California Pacific Medical Center, San Francisco.

164 **Selective Deafness**

SIMON AUSTER, MD, JD

From the F. Edward Hébert School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland.

OTHER FEATURES

103 **Subscription Information**

106 **Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming**

165 **In Memoriam**

166 **Instructions for Authors**

168 **Business and Subscription Information**

169 **Classified Advertising Order Form**

170 **Classified Advertising**

176 **Western State Medical Associations' Meetings**

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

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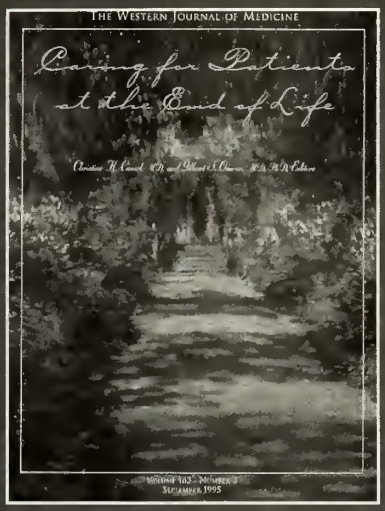

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

October 7-10—**Visiting Fellowships in MRI.** University of Arizona College of Medicine at the Biltmore Advanced Imaging Center, Phoenix. Mon-Thurs. Contact: (800) 848-4920, ext 2575.

October 14-18—**Neuroradiology: Review and Update.** University of Arizona College of Medicine at the Biltmore Advanced Imaging Center, Phoenix. Mon-Fri. Contact: (800) 848-4920, ext 2575.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

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U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (520) 626-7832; (800) 328-5868.

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This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

November 8-10—**8th Annual Anesthesiology Update: 1996.** UCD at Monterey Plaza Hotel, Monterey. 14 hrs. $350. Contact: UCD.

January 8-11—**Anesthesiology Update 1997.** UCSD at Hotel del Coronado, Coronado, Wed-Sat. 21 hrs. $375. Contact: UCSD.

January 31-February 2—**35th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Los Angeles at Sheraton Universal Hotel, Universal City. 15 hrs. $295. Contact: David J. Stewart, MB, Prog. Dir., Pediatric Anesthesiology Conf., Children's Hospital Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

CARDIOLOGY

October 10-12—**Cardiology Update 1996.** American College of Cardiology at Carmel Valley Ranch Resort. Thurs-Sat. 12 hrs. Contact: Registration Secretary, Extramural Programs Dept, ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814. (800) 253-4636.

October 17-19—**15th Annual Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 17 hrs. $475. Contact: UCSF.

November 2—**Update in Electrocardiography and Arrhythmias.** UCSF at AHA Hotel, San Francisco. Sat. 7.5 hrs. $175. Contact: UCSF.

November 22-24—**Coronary Heart Disease Update.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sun. 11 hrs. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4569. (800) 421-3756.

December 13-15—**14th Annual Advances in Heart Disease.** American College of Cardiology at San Francisco. Contact: ACC, (800) 253-4636, ext 695.

January 24-26—**Clinical Nuclear Cardiology: Case Review With the Experts.** American College of Cardiology at Los Angeles. Fri-Sun. Contact: ACC, (800) 253-4636, ext 695.

DERMATOLOGY

October 5-9—**11th Combined Skin Pathology Course and Workshop in Dermatopathology.** UCSD at San Diego Princess. Sat-Wed. 37 hrs, $600. Contact: UCSD.

October 17-20—**Minimally Invasive Techniques for Facial Rejuvenation.** UCSF at Embarcadero Hyatt Regency Hotel, San Francisco. Thurs-Sun. Contact: UCSF.

November 2-3—**The Skin From A to Z: Tips on Practical Therapy and Office Techniques.** UCSF. Sat-Sun. Contact: UCSF.

January 31-February 2—**Primary Care Dermatology.** UCSD at San Diego Hilton Beach and Tennis Resort. Fri-Sun. Contact: UCSD.

EMERGENCY MEDICINE

October 17-19—**15th Annual Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 17 hrs. $475. Contact: UCSF.

October 18-20—**The Comprehensive Review in Emergency Medicine and Urgent Care.** Continuing Medical Education Associates at Hyatt Regency, La Jolla. 20 hrs, $495. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

October 20-23—**Cellular Injury and Brain Edema, 1996.** Foundation for Pediatric and Laser Neurosurgery, Inc, at Hyatt Regency Hotel, San Diego. Sun-Wed. 19 hrs, $350-$400. Contact: Hector E. James, MD, Coordinator, Foundation for Pediatric and Laser Neurosurgery, Inc, 7930 Frost St, Ste 304, San Diego 92123. (619) 560-4791.

October 21-25—**Emergency Medicine Symposium I.** UCSD. Mon-Fri. 32 hrs, $495. Contact: UCSD.

October 28-November 1—**25th Annual Topics in Emergency Medicine.** UCSF at Holiday Inn, Union Square, San Francisco. Mon-Fri. 32 hrs. $655. Contact: UCSF.

November 11-15—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs, $495. Contact: UCSD.

December 7-8—**Stabilization and Management of the Critically Ill Child.** UCSF at Mark Hopkins Hotel, San Francisco. Sat-Sun. Contact: UCSF.

December 16-20—**Emergency Medicine Symposium II.** UCSD. Mon-Fri. 32 hrs, $495. Contact: UCSD.

February 1-21—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton Beach and Tennis Resort. 32 hrs. $495. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

October 9-11—**Primary Care Medicine: Principles and Practice.** UCSF at AHA Hotel, San Francisco. Wed-Fri. 20 hrs. $525. Contact: UCSF.

October 9-12—**Semiannual Wound Management Workshop: For Primary Care Professionals.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sat. 17 hrs. $475. Contact: UCSD, Edith Bookstein, (619) 454-3212.

October 17-20—**Office Based Orthopaedics for the Primary Care Physician.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 18.5 hrs. $395-450. Contact: UCSF.

(Continued on Page 107)

CONTINUING MEDICAL EDUCATION

(Continued from Page 106)

October 19—**Symposium on Women's Health.** UCD at UCD Medical Center, Sacramento. Sat. 7 hrs. $70. Contact: UCD.

October 21—**OB/GYN Pathology.** USC at Red Lion Hotel, Glendale. Mon. 8 hrs. $185. Contact USC.

October 21-23—**Neurology and Outpatient Psychiatry in Primary Care.** Continuing Medical Education Associates at Hyatt Regency, San Diego. 20 hrs, $450. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

November 15-17—**Women's Health Issues in Primary Care.** UCSD at Hilton Hotel, San Diego. Fri-Sun. 17.5 hrs. Contact: UCSD.

November 17-19—**3rd Annual Western Retreat: Practical Primary Care.** Scripps Clinic and Research Foundation at Silverado, Napa. Sun-Tues. 12 hrs. Contact: Scripps, (619) 554-8556.

December 5-6—**Controversies in Women's Health.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Fri. 13 hrs. $355. Contact: UCSF.

December 7-8—**Stabilization and Management of the Critically Ill Child.** UCSF at Mark Hopkins Hotel, San Francisco. Sat-Sun. Contact: UCSF.

January 17-19—**Practical Dermatology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Regency, La Jolla. Mon-Wed. 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego 92198. (800) 993-2632 or (619) 674-5200.

January 31-February 2—**Primary Care Dermatology.** UCSD at San Diego Hilton Beach and Tennis Resort. Fri-Sun. Contact: UCSD.

February 14-16—**Office Gynecology and Women's Health for the Primary Care Physician.** CMEA at Hyatt Islandia, San Diego, Fri.-Sun. 20 hrs. $475. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego 92198. (800) 993-2632 or (619) 674-5200.

February 17-19—**Clinical Hematology and Oncology: 1997.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Scripps, (619) 554-8556.

INFECTIOUS DISEASE

October 26-November 2—**National Infectious Disease Update Conference.** Santa Rosa Kaiser Permanente Medical Center on the Sun Princess Cruise, Western Caribbean. Sat-Fri. 7 hrs, $50-$100. Contact: Infectious Disease Update/SRO, Kaiser Permanente Medical Center, 401 Bicentennial Way, Santa Rosa 95403-2192.

December 5-7—**Clinical Care of the AIDS Patient.** UCSF at Sheraton Place Hotel, San Francisco.Thurs.-Sat. 24 hrs. $395. Contact: UCSF.

February 6-8—**Epidemiology and Prevention of Infectious Diseases.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

INTERNAL MEDICINE

December 8—**Endocrine Tumors: 101st Semi-Annual Cancer Seminar.** California Tumor Tissue Registry at Ritz-Carlton Hotel, San Francisco. Sun. 8 hrs. $265. Contact: CTTR, (909) 824-4788.

February 12-14—**Recent Adventures in Neurology.** UCSF at Hyatt Regency Hotel, San Francisco. Wed-Fri. 15 hrs. Contact: UCSF.

February 17-20—**Clinical Hematology and Oncology: 1997.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Scripps, (619) 554-8556.

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(Continued on Page 108)

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(Continued from Page 107)

OCCUPATIONAL MEDICINE

October 21-25—**Occupational and Environmental Medicine II.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $725. Contact: UCSF.

December 5-6—**Occupational Disorders of the Upper Extremities.** UC Berkeley at San Francisco Airport Hilton Hotel. Thurs-Fri. Contact: UC Berkeley.

ONCOLOGY

October 10-12—**20th Annual Physicians Cancer Symposium.** Scripps-Health at Sheraton Harbor Island Hotel, San Diego. Thurs-Sat. 17 hrs, $425-$450. Contact: Stevens Cancer Center, Scripps Memorial Hospital, PO Box 28, La Jolla 92038-0028; Ruthanne Crawford, (619) 626-6794.

October 19—**15th Annual Cancer Memorial Symposium—Winning Strategy Against Cancer.** Victor Valley Community Hospital at Holiday Inn, Victorville. Sat. 8 hrs, $90. Contact: Hi Desert Joint Cancer Program, Alice Williams, CTR Victor Valley Community Hospital, 15248 11th St, Victorville 92392. (619) 245-8691, ext 3432.

February 17-20—**Clinical Hematology and Oncology: 1997.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Scripps, (619) 554-8556.

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October 17-20—**Minimally Invasive Techniques for Facial Rejuvenation.** UCSF at Embarcadero Hyatt Regency Hotel, San Francisco. Thurs-Sun. Contact: UCSF.

October 19-23—**Temporal Bone Surgical Dissection Courses.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, (213) 483-4431, ext 7079.

October 31-November 1—**Facial Plating in Craniomaxillary Surgery.** UCD at Hyatt Regency Hotel, Sacramento. Thurs-Fri. 13 hrs. $150. Contact: UCD.

November 7-9— **Otolaryngology Update: 1996.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. 18.5 hrs, $425. Contact: UCSF.

November 9-13—**Temporal Bone Surgical Dissection Courses.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, (213) 483-4431, ext 7079

December 7-11—**Temporal Bone Surgical Dissection Courses**. The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, (213) 483-4431, ext 7079.

January 4-8—**Temporal Bone Surgical Dissection Course.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, 2100 W Third St, Los Angeles 90057. (213) 483-4431, ext 7079.

February 1-5—**Temporal Bone Surgical Dissection Course.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs. $1,300. Contact: House Ear Institute, (213) 483-4431, ext 7079.

PEDIATRICS

November 9—**Pediatric Pain Management in Managed Care Environment**. Children's Hospital and Health Center at Corning Labs Conference Center, San Diego. Sat. 7 hrs, $85. Contact: Children's Hospital, Continuing Medical Education, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

December 7—**Fifteenth Annual Binational Pediatric Conference.** Children's Hospital and Health Center at Mercy Hospital Education Center, San Diego. Saturday. 5 hrs, $45. Contact: Children's Hospital, Continuing Medical Education, 3020 Children's Way (5021), San Diego, 92123. (619) 576-4072.

December 7-8—**Stabilization and Management of the Critically Ill Child.** UCSF at Mark Hopkins Hotel, San Francisco, Sat.-Sun. Contact: UCSF.

January 15-18—**San Diego Cerebral Palsy Symposium.** Children's Hospital at San Diego Marriott Mission Valley. Wed-Sat. 21.5 hrs, $450-$495. Contact: Continuing Medical Education, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

January 27-31— **San Diego Conference on Responding to Child Maltreatment.** Children's Hospital at Town and Country Hotel, San Diego. Mon-Fri. 30.5 hrs, $435. Contact: Registration Coordinator, Center for Child Protection, 3020 Children's Way (MC5016), San Diego 92123. (916) 495-4940.

January 31-February 2—**35th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Los Angeles at Sheraton Universal Hotel, Universal City. 15 hrs. $295. Contact: David J. Stewart, MB, Program Dir, Pediatric Anesthesiology Conf., Children's Hospital Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

February 28-March 2—**Current Concepts in Pediatric Medicine—10th Anniversary.** Children's Hospital and Health Center at San Diego Hilton Beach and Tennis Resort. Fri-Sun. 16 hrs. $365. Contact: Children's Hospital, CME, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

PLASTIC SURGERY

October 12-13—**New Directions in Lasers and Cosmetic Surgical Procedures.** UCD. Sat-Sun. 13 hrs. $750. Contact: UCD.

October 17-20—**Minimally Invasive Techniques for Facial Rejuvenation.** UCSF at Embarcadero Hyatt Regency Hotel, San Francisco. Thurs-Sun. Contact: UCSF.

PSYCHIATRY AND NEUROLOGY

November 2-3—**Neurology Update.** UCSD at Hotel del Coronado, Coronado. Sat-Sun. 12 hrs, $350. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

November 8-10—**The 42nd Annual Group Therapy Symposium.** UCSF at Mark Hopkins Hotel, San Francisco. Fri-Sun. Contact: UCSF.

February 12-14—**Recent Adventures in Neurology.** UCSF at Hyatt Regency Hotel, San Francisco. Wed.-Fri. 15 hrs. Contact: UCSF.

RADIOLOGY

October 24-25—**Neuroradiology Comprehensive Review.** UCSD at Hotel del Coronado, Coronado. Thurs-Fri. 25 hrs, $550. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

October 26-27—**16th Annual Comprehensive Review of Vascular & Interventional Radiology.** UCSD at Hotel del Coronado, Coronado. Sat-Sun. 14 hrs, $375. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

October 28-November 1—**21st Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, Coronado. Mon-Fri. 27 hrs, $575. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

SURGERY

October 31-November 1—**Facial Plating in Craniomaxillary Surgery.** UCD at Hyatt Regency Hotel, Sacramento. Thurs-Fri. 13 hrs. $150. Contact: UCD.

January 4-8—**Temporal Bone Surgical Dissection Course.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, 2100 W Third St, Los Angeles 90057. (213) 483-4431, ext 7079.

UROLOGY

November 3-7—**VII World Meeting on Impotence.** American Urological Association and UCSF at Sheraton Palace, San Francisco. Mon-Thurs. $400-$475. Contact: UCSF.

GENERAL/MULTIDISCIPLINARY

October 18—**ACLS Recertification.** American Heart Association at San Francisco. Fri. 6 hrs, $100. Contact: CPR Seminars, (510) 632-6135.

October 19-20—**ACLS Provider.** American Heart Association at San Francisco. Sat-Sun. 16 hrs, $170. Contact: CPR Seminars, (510) 632-6135.

October 29-31—**ABC's Second Annual Telemedicine and Telehealth Con-**

(Continued on Page 109)

(Continued from Page 108)

ference. UCD at Anaheim Convention Center. Tues-Thurs. $450-$550. Contact: UCD, (800) 829-3400.

November 8—**Assault Prevention for the Healthcare Provider.** CPR Seminars at San Leandro. Fri. 5 hrs. $96. Contact: CPR Seminars, (510) 632-6135.

December 12-14—**Diagnosis and Treatment of Back Pain—The Next Level.** St Mary's Hospital at Stanford Court Hotel, San Francisco. Thurs-Sat. Contact: Aubrey A. Swartz, MD, American Back Society, St Joseph's Professional Center, 2647 E 14th St, Ste 401, Oakland 94601. (510) 536-9929.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

October 28-November 1—**42nd Annual Family Practice Review (Repeat of June program).** University of Colorado Health Sciences Center at Denver. Mon-Fri. Contact: U of Colo.

December 6-7—**5th Update in Infectious Disease: Bugs and Drugs in the '90s.** University of Colorado Health Sciences Center at Denver. Fri-Sat. Contact: U of Colo.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

October 10-13—**The Managed Care Tool Box.** Pyramid Hotel, Albuquerque. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

October 12—**Southwestern Regional Gastroenterology Symposium.** UNM Health Sciences Center Nursing/Pharmacy Auditorium, Albuquerque, Sat. Contact: UNM Office of Continuing Medical Education. (505) 277-3942. FAX (505) 277-8604.

October 25-26—**ECG Interpretation for the Primary Care Physician.** Journal Center, Albuquerque. Fri-Sat. Contact: Megan Slane, Course Coordinator, New Mexico Heart Institute, 1001 Coal Ave, SE, Albuquerque 87106. (505) 841-1000; (800) 715-6644. FAX (505) 224-7085.

December 11-14—**The Veterans Caucus 5th Annual Topics in the Tropics.** Sol Melia Beach and Spa Resort, Cancún, Mexico. Wed.-Sat. Contact: Sharon Hanley, RMP, Conference Coordinator, Geisinger Clinic, 100 N. Academy Ave., Danville, PA 17822-1350.

February 28-March 1—**25th Annual New Mexico Thoracic Society Lung Disease Symposium.** Taos. Fri-Sat. Contact: Billie Dytzel, 216 Truman NE, Albuquerque 87108. (505) 265-0732; (800) 221-LUNG. FAX (505) 260-1739.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

October 10-13—**Intensive Interactive Head and Neck Imaging**. University Park Hotel, Salt Lake City. Thurs-Sun. 30 hrs. $750. Contact: UUSM.

December 6-12—**Intensive MR Imaging and Neuroradiology**. Marriott Hotel, Salt Lake City. Fri-Thurs. 30 hrs. $1,250. Contact: UUSM.

February 5-9—**3rd Annual Brigham & Women's Utah Therapeutic GI Endoscopy Course 1996: Problems and Solutions.** Park City. Contact: UUSM.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

(Continued on Page 110)

(Continued from Page 109)

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.

DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.

ETS: Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.

FHP: FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UANS: Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

October 9–10—**11th Annual Lung Conference**. Seattle. Fri. Contact: Providence/Seattle Medical Center (206) 320-2552.

October 10—**And the Beat Goes On: Diagnosis, Management and Malpractice in Myocardial Infarction**. Vancouver. Thur. Contact: Physicians' Insurance (206) 343-6526.

October 10—**Preventing Misadventures in Anesthesiology**. Bellevue. Thur. Contact: Physicians' Insurance (206) 343-6526.

October 11–12—**PEARL Conference**. Seattle. Fri.-Sat. Contact: Children's Continuing Medical Education (206) 526-2501.

October 15—**Assessing Your Practive to Mimize Liahility**. Leavenworth. Tues. Contact: Physicians' Insurance (206) 343-6526.

October 17—**Tools for the Prompt Diagnosis of Colorectal and Prostate Cancer**. Longview. Thur. Contact: Physicians' Insurance (206) 343-6526.

October 18—**ACLS Renewal Course**. Seattle. Fri. Contact: Swedish Medical Center (206) 386-2265.

October 18–19—**Orthopedic Symposium**. Seattle. Fri.-Sat. Contact: Children's Continuing Medical Education (206) 526-2501.

October 24—**OB/GYN**. Everett. Thur. Contact: Providence General Medical Center (206) 261-3960.

October 24–26—**Breast Cancer**. Seattle. Thur.-Sat. Contact: U/W CME (206) 543-1050.

October 25—**Eighth Annual Current Concepts in Perinatology**. Tacoma. Fri. Contact: Multicare Health System CME (206) 552-1221.

October 25–26—**Mental Health Update**. Seattle. Fri.-Sat. Contact: U/W CME (206) 543-1050.

October 26—**Practical Pediatrics**. Seattle. Sat. Contact: Children's Continuing Medical Education (206) 526-2501.

November 1—**Orthopedics for the Non-Orthopedist**. Seattle. Fri. Contact: Swedish Medical Center (206) 386-2265.

November 2—**ACLS Renewal Course**. Seattle. Sat. Contact: Swedish Medical Center (206) 386-2265.

November 2—**Alternative and Complementary Medicine**. Seattle. Sat. Contact: Northwest Hospital (206) 364-0500.

November 6—**Emerging Infections**. Seattle. Wed. Contact: Providence/Seattle Medical Center (206) 320-2552.

November 6—**Infectious Disease Conference**. Seattle. Wed. Contact: Swedish Medical Center (206) 386-2265 (Co-sponsor with Providence/Seattle Medical Center).

November 6—**Worker's Compensation Care**. Bellevue. Wed. Contact: Group Health Cooperative of Puget Sound (206) 326-3441.

November 7—**And the Beat Goes On: Diagnosis, Management and Malpractice in Myocardial Infarction**. Olympia. Thur. Contact: Physicians' Insurance (206) 343-6526.

November 7—**Tools for the Prompt Diagnosis of Colorectal and Prostate Cancer**. Silverdale. Thur. Contact: Physicians' Insurance (206) 343-6526.

November 7–8—**Current Advances in Drug Therapy**. Seattle. Thur.-Fri. Contact: U/W CME (206) 543-1050.

November 7–8—**NIOSH 596: Ergonomics of Occupational Hand-Arm & Whole-Body Vibration**. Seattle. Thur.-Fri. Contact: U/W Dept. of Environmental Health (206) 543-1069.

November 9–10—**Advance TCD Course on Perioperative and Embolism Monitoring**. Seattle. Sat.-Sun. Contact: Providence/Seattle Medical Center.

November 12–13—**NIOSH 596: Ergonomics of Occupational Hand-Arm & Whole-Body Vibration**. Seattle. Thur.-Fri. Contact: U/W Dept. of Environmental Health (206) 543-1069.

November 12–13—**Chronic Care/Senior Care Management 1996**. Seattle. Thur.-Fri. Contact: Group Health Cooperative of Puget Sound (206) 326-3441.

November 13—**Assessing Your Practice to Minimize Liability**. Issaquah. Fri. Contact: Physicians' Insurance (206) 343-6526.

November 14—**Important Topics in the Management of Patients During Shipt to Outpatient Medicine**. Everett. Thur. Contact: Providence General Medical Center (206) 261-3960.

November 14—**GI Medications Conference**. Seattle. Thur. Contact: Swedish Medical Center (206) 386-2265.

November 14—**Malpractice Prevention Under Managed Care**. Spokane. Thur. Contact: Physicians' Insurance (206) 343-6526.

November 14—**Preventing Misadventures in Anesthesiology**. Seattle. Thur. Contact: Physicians' Insurance (206) 343-6526.

November 15—**Psychiatric Issues for Primary Care**. Seattle. Fri. Contact: Virginia Mason (206) 223-6898.

November 22—**Psychiatry Symposium**. Seattle. Fri. Contact: Providence/Seattle Medical Center (206) 320-2552.

November 22—**Pinkham Basic Science Lectureship**. Seattle. Fri. Contact: Swedish Medical Center (206) 386-2265.

December 3—**Tools for the Prompt Diagnosis of Colorectal and Prostate Cancer**. Seattle. Tues. Contact: Physicians' Insurance (206) 343-6526.

December 6—**17th Annual Pediatrics Conference**. Seattle. Fri. Contact: Virginia Mason (206) 223-6898.

December 12—**And the Beat Goes On: Diagnosis, Management and Malpractice in Myocardial Infarction**. Mt. Vernon. Thur. Contact: Physicians' Insurance (206) 343-6526.

December 12–14—**Annual Meeting: Washington State Chapter American College of Physicians**. Seattle. Thur.-Sat. Contact: U/W CME (206) 543-1050.

December 12–14—**The 12th Annual Infectious Disease Conference**. Seattle. Thur.-Sat. Contact: PNCEI (360) 653-4543.

December 13—**Alternative Medicine 1996**. Bellevue. Fri. Contact: Group Health Cooperative of Puget Sound (206) 326-3441.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

(Continued on Page 111)

CONTINUING MEDICAL EDUCATION

(Continued from Page 110)

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

OTHER CME OPPORTUNITIES

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

CREIGHTON UNIVERSITY SCHOOL OF MEDICINE. November 21–22—**Nebraska Symposium on Cancer and Smoking Related Diseases**. Omaha.Thu.-Fri. Contact: Sally C. O'Neill, PhD, Associate Dean, Creighton University CME Division, 601 North 30th St., Suite 2130, Omaha, NE 68131. (800) 548-CMED or (402) 280-1830.

CREIGHTON UNIVERSITY SCHOOL OF MEDICINE. July 9–11, 1997—**14th Annual Scientific Session of the American Association of Clinical Anatomists**. Honolulu. Wed–Fri. Contact: Sally C. O'Neill, PhD, Associate Dean, Creighton University CME Division, 601 North 30th St., Suite 2130, Omaha, NE 68131. (800) 548-CMED or (402) 280-1830.

CREIGHTON UNIVERSITY SCHOOL OF MEDICINE. July 12, 1997—**Clinical Anatomy of the Basic Physical Examination**. Honolulu. Sat. Contact: Sally C. O'Neill, PhD, Associate Dean, Creighton University CME Division, 601 North 30th St., Suite 2130, Omaha, NE 68131. (800) 548-CMED or (402) 280-1830.

NOTICE

State Associations should send their CME listings for publication to:

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Articles

Torture and War Trauma Survivors in Primary Care Practice

HARVEY M. WEINSTEIN, MD, MPH; LAURA DANSKY, PhD;
and VINCENT IACOPINO, MD, PhD, *San Francisco, California*

Close to 1 million refugees from around the world have entered the United States, fleeing repression, war, terrorism, and disease. It has been estimated that among these are thousands who have experienced torture. Many refugees and immigrants will appear in the offices of health care professionals with symptoms that may be related either directly or indirectly to torture. Both physical and psychological torture may result in long-term sequelae. Physical effects may be found in every organ system, but psychological effects are most commonly manifest in the symptoms of the post-traumatic stress disorder. For physicians to recognize how torture can affect health status, it is important to understand that history taking may be difficult and that little information may emerge that would explain the origins of scars, fractures, or disabilities. Recognizing the clues to a torture history allows physicians to assist patients in describing the trauma. In addition, knowing the subacute and chronic signs and symptoms of torture enables physicians to diagnose and treat often obscure symptoms with a much clearer understanding of the sources of the difficulty. Paying special attention to the interview process will support torture survivors in detailing often horrific events.

(Weinstein HM, Dansky L, Iacopino V: Torture and war trauma survivors in primary care practice. West J Med 1996; 165:112–118)

As newspaper accounts and photographs of torture, mass graves, rape, flight, and fear force us to recognize the plight of much of humanity, it is apparent that a substantial number of the world's refugees will appear in the United States and, ultimately, in the offices and examining rooms of health care professionals. It is critical to ask, What are the health effects of the physical and emotional trauma experienced by these men, women, and children? In addition, how can the sensitivity of primary care physicians in history-taking situations be enhanced so as to both elicit information about the trauma and offer support to those who have been so brutalized? For these patients, medical examinations may be fraught with anxiety for unique reasons. Physicians may have been involved in their torture, and examination tools and procedures may precipitate memories of the torture implements or methods. An authoritarian interaction between physician and patient as well as language difficulties may cause acute emotional reactions or profound withdrawal. Consequently, information required for diagnosis, treatment, and preventive interventions may be missed. Our rapidly changing world requires that we become aware of the context in which our multicultural population has arrived in the United States. In this article, we address how the risk factors of refugee status and torture or trauma influence health status.

Displaced Peoples

It has been estimated that there are 50 million refugees in the world, of whom 23 million have been forced to flee their countries of origin.[1,2] Men and women, elderly persons, children, and adolescents must confront the loss of home, family, culture, language, and all that represented stability and security. Malnourished and sometimes diseased, they may have lived in chaotic camps, further exposing them to violence and intimidation. Some of the following factors that lead up to the decision to flee have been described: political repression, detention, torture, terrorism, disappearances of family and friends, loss, and exile.[3(pp7–10)] From 5% to 35% of the world's refugees have been estimated to have experienced torture,[4(p85)] which, given the above figures, suggests that the population at risk lies between 1.1 and 8 million. To these must be added the substantial number of internally displaced people who have been the recipients of torture. Many others, although not directly tortured, have been exposed indirectly as family or friends of those who have been abused.

Torture

Torture in this context does not refer to domestic or street violence. Rather, it is a process of brutal human degradation that occurs in a setting of political repres-

From Survivors International (Drs Weinstein, Dansky, and Iacopino) and the Western Regional Office of Physicians for Human Rights (Dr Iacopino), San Francisco, California.

Reprint requests to Harvey M. Weinstein, MD, MPH, Human Rights Center, University of California, Berkeley, Berkeley, CA 94720-2340.

sion or state-sponsored terrorism. The World Medical Association, in its Declaration of Tokyo (1975), defines it as follows:

> Torture is . . . the deliberate, systematic, or wanton infliction of physical or mental suffering by one or more persons, acting alone or on the orders of any authority, to force another person to yield information, to make a confession, or for any other reason.

The United Nations Convention Against Torture (1984) notes that torture may take the form of physical or mental abuse, it is intentional, and it has a larger goal. "[S]uch pain or suffering is inflicted by or at the acquiescence of or with the consent of a public official or other person acting in an official capacity." Examples of this come readily to mind: Chile, Argentina, El Salvador, Guatemala, South Africa, and others.[5] An epidemiology of torture is difficult to develop because it is carried out in secret and suppressed from public knowledge. Without the work of such organizations as Amnesty International, Physicians for Human Rights, or Human Rights Watch, little would be known. In an analysis of 1992 Amnesty International data from sources as diverse as ex-prisoners, family members, and lawyers,[6] it was determined that "systematic torture and/or ill treatment" is carried out in 93 countries of the world.[7]

Sergio Pesutic, a Chilean physician, has described torture as "the dehumanized use of power."[8] Torture is thus an instrument of oppression, it is state-sponsored, and it is a display of overwhelming power on a personal level.

Why do states torture, and how does it affect its victims? The following five purposes have been suggested for torture[9]: information gathering, the incrimination of others, the indoctrination of the government's political belief system, intimidation, and isolation (from colleagues or similarly minded antigovernment comrades). Torture usually occurs in a context where social and psychological factors have coalesced to allow the dehumanization and negative labeling of targeted groups and where obedience to orders or authorization by the government becomes the reason to act, usually under the guise of patriotism.[10] Aside from the many physical sequelae of torture, the process is designed to render its victims nonhuman. Torture destroys the self and the very foundations of stability; the person undergoing torture can believe in nothing; questions of morality become irrelevant; decisions may become impossible choices; and survival may mean either forced betrayal or lifelong guilt. In a classic paper on brainwashing, three components were noted to be required for breaking down someone's resistance: debility, dependency, and dread.[11] Even with the utmost of human resiliency, long-term effects of these experiences are likely.

Why Is This Important to American Physicians?

Up to now, the United States has welcomed most of the world's legal immigrants and refugees. California has received more of this population than any other state. From 1985 to 1992, 810,750 refugees and asylees were granted US permanent resident status, and more than 7 million legal immigrants arrived during the 1980s.[12(pp80,81,89)] In 1990 it was estimated that about 600,000 refugees lived in California (almost a third of the nation's total).[13] As well, it was estimated that 1 of 50 Californians was a refugee. A substantial number of refugees are found throughout the western states.

The major population groups have come from Southeast Asia, Latin America, and eastern Europe. A large number of these refugees have experienced torture in such diverse places as Cambodia, Vietnam, the Philippines, Argentina, Uruguay, Chile, El Salvador, Guatemala, India, the former Yugoslavia, countries of the former USSR, Ethiopia, Eritrea, Zaire, Somalia, Kenya, South Africa, and many of the Middle Eastern states. Along with the multitude of skills and hope that they bring, they carry a legacy of guilt and terror. A simple Pap smear may awaken a memory of sexual trauma at the hands of militia; a bright light in the eye can bring forth a memory of interrogation; a question about scars may elicit profound fear of being reported to government authorities.

To provide comprehensive care, physicians must become aware of the possibility of torture in a refugee's or immigrant's history and develop the ability to recognize physical signs that indicate that torture has occurred. From our clinical experience with more than 300 refugee survivors of torture and from the relevant literature,[14] we propose a set of risk factors the presence of which in a history are suggestive of the possibility that a patient may have been tortured (Table 1).

TABLE 1.—*Historical Risk Factors for Torture*

Refugee or political asylee status
Immigrant from country with totalitarian history
Member of minority group in country of origin
Member of minority political party in country of origin
Civil war in country of origin
Residence in refugee camp
Military government in country of origin
Prisoner of war
Flash-point country—that is, Bosnia, Somalia, Rwanda
Multiple family members deceased due to trauma
History of arrest or detention
Leadership in an antigovernment organization or relative of same

Methods of Torture

Torture may include both physical and psychological methods, although they cannot always be separated. For example, hooding impedes normal breathing but also produces disorientation and fear. Tables 2 and 3 illustrate

common torture methods described by several authors.[3(pp8–9),15–17] Although there is much similarity of methods around the world, especially in a regional context, there is also variation. Survivors may be unable to describe exactly what happened to them because they may have been blindfolded, lost consciousness, sustained head injury, or have difficulty recalling or revealing the especially traumatic components of their experience.

The list given in Table 2 is not exclusive, and other forms of torture, such as stretching on a rack, are still used. Sexual torture is common[18] and, not surprisingly, often underreported by men and women. The use of implements and animals to humiliate and destroy the will often produce intense shame and a need for concealment.

Torturers often attempt to conceal their acts. To avoid physical evidence of beating, torture is often performed with a wide, blunt object, and victims are sometimes covered with a rug—or shoes, in the case of falanga (beating the soles of the feet)—to distribute the force of individual blows. Stretching, crushing injuries, and asphyxiation are also forms of torture that produce maximal pain with minimal evidence. For the same reason, wet towels may be used with electric shocks.

Psychological torture is part and parcel of physical abuse as well. Specific psychological methods have been honed through the years that are specially designed to promote "debility, dependency, and dread" so as to break people down. Included in these are sensory deprivation (isolation, hooding, constant noise, darkness), the restriction of physiologic needs (food, water, sleep, toilet), and social isolation. Added to these are humiliation in word and deed, overcrowding, filth, sexual abuse, threats, the use of drugs to distort reality or compromise breathing, and the use of psychological interrogation techniques that reinforce helplessness, such as abusing victims regardless of their responses to the interrogation.

TABLE 2.—*Some Common Methods of Physical Torture**

Method	*Examples†*
Beatings	Hitting, clubbing, kicking—whole body or specific parts (head, genitalia)—with fists, clubs, rifles; *telefono, falongo, plonton*, stabbings, and razor cuts
Electric shock	Cattle prod, multiple electrodes, electrically charged bedspring (to breasts, genitals, anus)
Burning	Cigarettes, cigars, other hot implements, wet and dry *submorino*, forced inhalation of chemicals
Asphyxiation	Wet and dry submarino, forced inhalation of chemicals
Stretching	Suspension by limbs, forced abduction of the legs
Genital torture	Blunt or penetrating trauma, electrical, vaginal or anal rape, animal rape
Other trauma	Fingernail and toenail removal, removal of teeth or dental fractures, prolonged exposure to heat or cold

*From van der Veer,[3] Rasmussen,[15] Randall and Lutz.[16]

†*Telefona* is simultaneous beating of the ears; *falanga* is beating of the soles of the feet; *plantan* is forced standing; wet *submarina* refers to the submersion of the head in contaminated water or other liquid or semiliquid waste, such as feces; dry *submarino* involves asphyxiation by a plastic bag or chemical inhalation.

TABLE 3.—*Some Common Forms of Psychological Torture**

- Threats—pain, torture, execution
- Isolation and uncertainty about release
- Sensory deprivation
- Mock executions
- Forced witnessing of beatings, rapes, or executions of friends or family
- Sleep deprivation
- Interrogation for hours
- Excessive noise

*From van der Veer[3] and Stover and Nightingale.[5]

Physical and Psychological Consequences of Torture

Given the number and variety of torture methods, widespread signs and symptoms are possible (Tables 4 and 5). Because most of the patients who present in the United States will no longer be in the acute post-torture state, we will describe some of the major subacute and chronic effects of torture.

Specific signs and symptoms may include scarring; hearing loss, with tears in the pars tensa; rib or other fractures; pulmonary tuberculosis; rectal bleeding; knee or vertebral problems; dysesthesia; plexopathy, especially brachial plexopathy; radiculopathies; hematuria and dysuria; and sexually transmitted diseases. Combining relevant facts in the history with more specific questions about torture will illuminate many of the physical findings and presenting symptoms. It should be kept in mind, however, that the degree of correlation between long-term signs and symptoms and specific torture methods is variable, and often the effects of torture may not be distinguishable from other diagnostic possibilities.

The most dramatic psychological consequence of torture and other extraordinary stressful events is the onset of the post-traumatic stress disorder. Recently revised by the American Psychiatric Association,[19] the case definition includes key components as shown in Table 6.

The full definition of the syndrome of PTSD can be found in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders.[19] Symptoms may antedate the trauma; patients may experience symptoms from several diagnostic categories. The manifestations of the post-traumatic stress syndrome may vary according to the culture and language of the person who has experienced the traumatic event. A recent study suggests that the severity and type of presenting symptoms may reflect how the torture was perceived by the survivor, the nature of the stressors after the torture, and finally, the degree of social support received by the survivor.[20]

Because most of those who have experienced torture have appeared in western countries after long histories of trauma, including uprooting, civil disturbance, and flight,

TABLE 4.—*Key Physical Consequences of Torture*

All organ systems may be affected
Psychosomatic and neurologic symptoms are most typical in chronic state
Musculoskeletal system symptoms are common in acute and chronic states
Falanga may result in subcutaneous fibrosis and a compartment syndrome of the feet
Electricity and various methods of burning—cigarettes, chemical—may leave characteristic skin changes
Whipping may leave a characteristic pattern of scars
Body suspension and stretching of limbs may result in characteristic musculoskeletal and nerve injuries—such as brachial plexopathies
Beatings to the head with loss of consciousness may contribute to organic brain dysfunction
Genital trauma is often associated with subsequent sexual dysfunction

TABLE 5.—*Key Psychological Consequences of Torture*

Post-traumatic stress disorder
Generalized anxiety disorder
Major depression
Psychosis or brief psychotic reactions
Chronic organic brain syndromes due to head trauma or asphyxiation; primarily attentional and cognitive difficulties
Substance and alcohol abuse
Sexual dysfunction

with superimposed acculturative stress, it is difficult to ascertain whether there is a "torture syndrome" separate from the effects of refugee trauma. In addition, as social epidemiologists have increasingly elucidated, the effects of a traumatic experience are a culmination of biologic predisposition, environmental stress, coping factors, and other mediating variables, such as a person's social support, that may serve as protective influences.[21-23] Consequently, we do not have a comprehensive picture of which torture survivors will have long-term problems develop and which will show a resilience that allows for normal lives. We do know that there is a generally complete picture of the health effects of refugee trauma,[24] and the separate effects of torture over and above other influences of political repression on Turkish activists, for instance, have recently been demonstrated.[25] Other researchers have examined the effects of culture on the post-traumatic stress disorder, a critical question when survivors arrive in America from many different backgrounds.[26-30] Given the complexity of these influences, it is important to emphasize that torture exists, and that over and above refugee trauma, it leaves physical and emotional scars that can be measured or observed. Symptom presentation is influenced by culture, and whether any given person experiences long-term problems is a result of complex interactions of history, biology, the nature of the stressor, and the support received.

Illustrative Case

"Susana" grew up in a large middle-class family of eight children. Two of her siblings were politically active, and when she was 14, one of her brothers was "disappeared." Over the next few years, several members of her extended family were arrested, tortured, and executed.

As a teenager, she was arrested without charge and brought to the office of the local militia. Interrogated and tortured daily, she was accused of aiding a rebel group. Beatings with fists, kicks, and whips occurred whether or not she gave any response. On most occasions, she was beaten bloody; often she was left unconscious. The torturers used a variety of techniques: she was suspended upside-down from a bar by her hands and ankles as her feet were beaten (*falanga*) and then forced to walk on sharp stones. Both ears were struck simultaneously with open fists (*telefono*), causing intense head pain. She experienced mock executions and forced confessions at gunpoint.

After a period of solitary confinement, she was placed in a small communal cell with 50 women. The women slept on a concrete floor with no heat, no toilet, no ventilation, and little light or food. Women were taken out and raped; some never returned. The women were humiliated in many ways. Susana was sexually abused and became suicidal. She remained in the cell for five months, during which time 20 of the women were killed.

After release, she eventually left her country, fearful of being rearrested. Her once-close family is now scattered all over the world. Soon after she arrived in California, a cousin concerned about Susana's depression, insomnia, and fearfulness referred her to our clinic. At first she was interested only in medical treatment of the chronic musculoskeletal pain in her knees and feet and of abdominal pain that was continuous. As her medical treatment proceeded, she began to talk about the experiences that had left her with these symptoms. As memories resurfaced, a suggestion was made that psychotherapy might be of help. Although ambivalent, she met with a Survivors International clinician and began the long process of healing.

Torture Survivors and Health Care Professionals

Given the nature of torture and the legacy of trauma, it is not surprising that torture survivors or victims of brutal wars bring to the medical visit vulnerabilities that influence the physician-patient interaction. At a minimum, there may exist a basic mistrust that makes the act of receiving care difficult. In addition, one study has reported that some 20% of torture survivors indicate the

TABLE 6.—*Post-Traumatic Stress Disorder**

Traumatic event

Experience or exposure to events involving actual or threatened death or serious injury, or a threat to the physical integrity of self or others

Response involved intense fear, helplessness, or horror

Reexperiencing or reliving of the initial event (≥1 of these)

Recurrent, intrusive, and distressing recollections of the event, such as images, thoughts, or perceptions

Recurrent distressing dreams of the event

Acting or feeling as if the traumatic event were recurring, that is, reliving, illusions, hallucinations, and dissociative flashback episodes

Great distress when exposed to cues that provoke memories of the trauma

Physiologic responses when exposed to cues that provoke memories of the experience

Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness

Patient avoids any activities, feelings, or anything that may provoke memories of the experience; survivors may avoid engaging in many of life's important activities and may not feel involved with others; they may experience a lack of feeling and a sense that they may not have a normal life course

Persistent symptoms of increased arousal

Sleep difficulties, anger, hypervigilance

*Adapted from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition.[19]

involvement of a physician in their torture.[15] Physicians who participate in torture may examine victims and report their weaknesses to the torturers; they resuscitate and treat them to allow further abuse; they falsify death certificates; and, despite the Hippocratic Oath or its equivalent, they do not overtly protest.

Many survivors are afraid to talk, especially about what happened, for fear of reexperiencing the trauma. They may be afraid of repercussions to themselves or family or of bringing pain to those they love. Some may fear not being believed or, if they are, of being ostracized—for example, if they were raped. Shame and guilt may interfere with acknowledging the torture experience.

Because survivors of torture have at one time felt so helpless, the act of placing themselves in the passive role with any authority figure such as a physician may provoke anger or withdrawal. Guarded histories may also reflect an attempt to protect the physician from the horror that they carry within. Psychosomatic symptoms may reflect the need to hide their heinous experience from themselves as well as others.

It is important for physicians to become aware of these vulnerabilities and to recognize that the patient-physician interaction can be structured in such a way as to minimize the stress and promote open responses. Good medical care for refugees and torture survivors depends on obtaining a complete history that reflects the trauma experience. Table 7 describes key issues that should be considered.

Training for health and mental health professionals is available through programs developed by such organizations as Survivors International and Physicians for Human Rights.

Conclusion

The treatment of patients who have had exposure to war violence and torture poses a special problem for primary care physicians. Symptoms of illness may be vague and persistent; signs of torture can be subtle and may be overlooked if patients cannot talk about the trauma. Physicians are faced with the dilemma of making a decision as to whether it is critical to pursue a line of questioning that may reveal horrors and memories that cause patients considerable pain. Yet, if the signs and symptoms suggest that trauma underlies the presenting problem, a physician is bound to explore the area in a gentle way that makes it clear that he or she is open to hearing the story. It is critical that if these questions are explored, there must be time set aside to do so. This may necessitate an additional visit. When the presenting symptom is not relevant to the torture history, it may be that exploration is optional. Clearly, however, in an ongoing therapeutic relationship, a shared knowledge of what happened will likely enable the physician to offer more comprehensive and thoughtful care for the patient.

It is important that patients not be retraumatized by the process of history taking. Physicians working with refugees who may have experienced torture can enhance their knowledge both by literature review and training. In addition, using the consultative or referral resources of mental health professionals trained to work with torture survivors results in a collaboration that can maxi-

TABLE 7.—*Interviewing Torture Survivors*

The Setting

As un–cell-like as possible

Comfortable climatic conditions

All objects in view (no screens)

Awareness that anxiety can be triggered by seemingly innocent objects

The Process

Waiting for appointments may trigger patient anxiety because of the remembered waiting for torture

Decrease anxiety by explaining who you are, what your role is, and how the interview and examination will work; it is critical to diminish the element of surprise, especially with certain examinations or treatments such as venipuncture or pelvic examination

Give patient some sense of control—for example, to take a break or use washroom

Questioning should be done gently

Questions should be tactful but direct—for example, "People with memory problems or bad dreams have often been tortured or traumatized. Is this something that has happened to you?"

Acknowledge that disclosure is difficult

Educate patient about symptoms—that it is common to feel that the symptoms are indications of mental illness; offer reassurance that these are normal reactions to abnormal events

Correct misperceptions—for example, sexual torture usually does not result in impotence or sterility

Interpreters

Use interpreters, but be aware that problems exist with using family members, fellow nationals, or North Americans who may miss cultural nuances; sensitivity is critical

Education

Teach about the North American health care system

Refer for psychological counseling and know referral centers

Refer for social services

mize the prospects of recovery. Various psychotherapeutic techniques and psychopharmacologic interventions have effectively alleviated war trauma symptoms.

It is not easy to learn about war trauma. It is more difficult to hear stories of torture. Even physicians who have been trained to hear and see the worst may not be prepared for the evil that humanity can impose on itself. It is not uncommon for those who treat torture survivors to experience depression, anxiety, nightmares, and irritability. A willingness to talk with colleagues about these patients goes a long way in ameliorating these responses. In addition, knowing the resources for patients affords physicians the opportunity to both learn about torture and find assistance in dealing with difficult issues.

Torture is one of the new epidemics that is sweeping the world. The mass migration of people across continents and over oceans means that we must be prepared to diagnose and compassionately treat the many survivors for whom the sanctuary of the United States can provide only partial safety. With our help, refugee survivors of torture may at last find some measure of security and well-being.

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Articles

Trends in California Homicide, 1970 to 1993

LAWRENCE D. CHU, MS, *and* SUSAN B. SORENSON, PhD, *Los Angeles, California*

In addition to the need to identify homicide trends among well-documented risk groups, this investigation was conducted to expand the limited existing knowledge about the risk of homicide according to educational attainment and among 2 growing ethnic groups, Hispanics and Asians. We examined the death certificates of the 69,621 persons who died of homicide in California from 1970 through 1993. Age, sex, race and ethnicity, and education level of the victim, along with the homicide method, were abstracted from each record. Frequencies, rates, and relative risk were calculated. Substantial increases in the homicide rates occurred for 15- to 19-year-olds (4.0-fold), men (1.9-fold), Hispanics (2.5-fold), and Asians or others (1.7-fold) from 1970 to 1993. The use of firearms consistently accounted for a growing proportion of all homicides, reaching a high in 1993 of 75% for all persons and 90% for 15- to 19-year-olds. High school dropouts have the highest homicide risk of all education groups. Homicide risk differentials by ethnicity, sex, and age all increased during the study period. Persons of color and youth have been disproportionately affected by homicide for many years, and these data indicate that things are getting worse. Redoubled collaborative prevention and intervention efforts are needed to reverse this trend.

(Chu LD, Sorenson SB: Trends in California homicide, 1970 to 1993. West J Med 1996; 165:119-125

Homicide is an increasing public health concern in the United States. It perennially ranks among the ten leading causes of death, and rates have been increasing since 1960 even as death rates from other causes have decreased.[1-5] The United States leads industrialized nations with the highest homicide numbers and rates; among 15- to 24-year-olds, the US homicide rate is more than four times the next highest rate.[6] The increased number of homicides and other intentional injuries is so alarming that violence was declared a public health emergency in 1992.[7]

Sex, race or ethnicity, and age have been associated with homicide risk, and firearms have been identified as a major external cause of homicide.[8-12] The highest homicide rates in the nation generally occur in men, African Americans, and 15- to 34-year-olds; in fact, homicide is the leading cause of death for young African-American men and women.[13] Geographic comparisons of homicide show high rates in the South and West and lowest rates occurring in the North and the Northeast.[14,15]

California is of particular interest because it has one of the highest rates in the United States, accounting for nearly one of every six homicides in the nation.[16] From 1986 to 1988, California reported homicide rates for young white men and young African-American men to be 92% and 67%, respectively, above the nation's average. Studying an ethnically diverse population such as California's will expand the knowledge about the homicide risk in groups about whom we know relatively little, specifically, Hispanics and Asians. Data on homicide trends and patterns in California will be useful in developing future studies targeting other risk factors and expanding our knowledge of homicide risk.

Methods

Study Population

The study population comprised the 69,621 persons who died of homicide in California from 1970 through 1993. California residents who died outside the state were excluded. Death certificate data were obtained through the California Master Mortality Data Tapes made available by the California Department of Health Services. Homicide deaths were identified using the eighth and ninth revisions of the *International Classification of Diseases* (ICD-8, ICD-9) external cause-of-death codes.[17,18]

Variables of Interest

The variables of interest from the death certificate data included sex, race, ethnicity, age, and education level of the victim and the method of homicide as identified through the ICD external-cause-of-death codes. Referent groups were established for each of the demographic variables for comparison and for calculating the relative risk.

Race and ethnicity were classified into four groups: non–Hispanic white, African American, Hispanic, and

From the School of Public Health, University of California, Los Angeles (UCLA).
This work was supported in part by a grant from the California Wellness Foundation.
Reprint requests to Susan B. Sorenson, PhD, UCLA School of Public Health, 10833 Le Conte Ave, Los Angeles, CA 90095-1772.

ABBREVIATIONS USED IN TEXT

CI = confidence interval
ICD = *International Classification of Diseases*
RR = relative risk

Asian and other based on three death certificate variables: race, Hispanic origin, and Spanish surname. Race categories on death certificates included black, white, Asian, American Indian, and other. California death certificates consistently used a Hispanic identifier beginning in 1987, which precluded the identification of Hispanics, a substantial portion of California's population[19] for much of the study period. For this reason, a Spanish surname file of 12,497 names from the US Bureau of the Census was compared with decedents' last names to identify Hispanic homicide victims.[20] An additional 2,064 surnames were added to the list to identify those who were missed by the original surname file but who were thought to be of Spanish descent (for example, hyphenated names such as Lopez-Garcia). African Americans and Asians were excluded from the surname linkage to reduce possible misclassification. Four ethnic-racial groups were created: black, white, Hispanic, and Asian or other.* Because of the relative stability of their homicide rate, non–Hispanic whites were used as the referent group for comparisons by ethnicity.

Age was categorized into ten groups: 0 to 4 years, 5 to 14 years, 15 to 19 years, 20 to 24 years, 25 to 34 years, 35 to 44 years, 45 to 54 years, 55 to 64 years, 65 to 74 years, and 75 years or older. Because most homicide victims are teenagers and young adults, the 15- to 24-year age group was divided into two 5-year age groups. The 35- to 44-year age group was used as a referent because the annual average homicide rate of that group closely parallels the annual overall homicide rate; it has one of the most stable homicide rates; it can be regarded as a transition period between youth and middle age and would highlight differential risks between the two; and better comparisons to youth homicide can be made with this group (than with, for example, 65- to 74-year-olds) because of the proximity in age.

Five categories of educational attainment were established for homicide victims aged 25 years or older: eighth grade or less, high school dropouts (grades 9 to 11), high school graduates (grade 12), some college (1 to 3 years), and college graduates (≥4 years of college). Denominator data for education status were obtained from the annual Current Population Surveys from the California Department of Finance and included persons aged 25 years or older only. Data on education level were available on death certificates starting in 1989, so relative risks were calculated for the 1989 to 1993 period. High school graduates were used as a referent group because of the relative stability of their homicide rates and because it was the modal education level.

The external cause of homicide (ICD E-codes) was separated into firearm or explosive (965), cutting or stabbing (966), and other (960 to 964, 967 to 969). Firearm and explosive homicides were treated as one category until 1976, when they were assigned separate categories. The number of homicides due to explosives is negligible compared with the number of firearm homicides; explosives consistently accounted for less than 0.5% of all firearm and explosive homicides after 1976.

*Population projections—that is, denominator data—for Native Americans were not available until 1990. Thus, an "Asian and other" group was used in the analyses.

Figure 1.—The California homicide rates for 1970 to 1993 are shown.

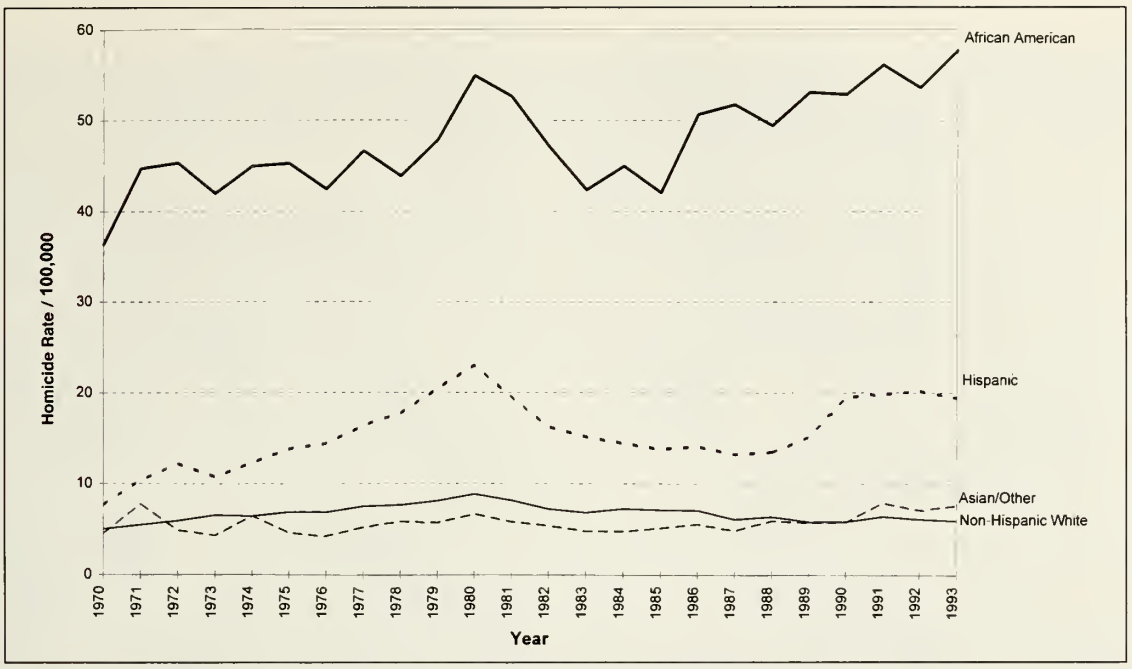

Figure 2.—The California homicide rates by race or ethnicity—African American, Hispanic, Asian or other, and non-Hispanic white—for 1970 to 1993 are shown.

Temporal variations in homicide frequency were examined by month and season: winter (January through March), spring (April through June), summer (July through September), and fall (October through December).

Denominator data for sex, race or ethnicity, age, and education level were based on estimates provided by the California Department of Finance.

Statistical Analysis

Frequencies were tabulated to compare homicide methods across time and to assess seasonal variations. Homicide rates per 100,000 persons and relative risks (RR; and their 95% confidence intervals [CI]) were calculated to examine homicide risk by sex, race and ethnicity, age, and education. Five time periods—1970 to 1974, 1975 to 1979, 1980 to 1984, 1985 to 1989, and 1990 to 1993—were used to facilitate comparisons across time.

Results

California's 1993 homicide rate of 13.4 per 100,000 is an 81% increase from the 1970 rate of 7.4, but is less than the 1980 peak of 14.8. The nation's homicide rate follows a similar trend observed in California data: increasing during the 1970s, peaking in 1980, decreasing in the early 1980s, and increasing again after 1985. California and US homicide rates by sex, race and ethnicity, and age groups also are relatively similar.

Homicide rates are higher among men than women, and the gender disparity is growing (Figure 1). The 1993 male homicide rate of 22.1 per 100,000 is 1.9 times the 1970 rate of 11.5 per 100,000. Although the annual rate change was relatively small, the 1993 female homicide rate was 1.3 times the 1970 rate, increasing from 3.6 to 4.7 per 100,000. The rate increase was not consistent; as can be seen in Figure 1, rates increased throughout the 1970s, decreased in the early 1980s, and increased relatively steadily to the end of the study period.

As shown in Figure 2, homicide rates differ substantially by ethnic group, and the difference between non–Hispanic whites and the three minority groups is also growing. African-American homicide rates are consistently higher than those of other groups; the 1993 rate of 57.7 per 100,000 is 1.6 times the 1970 rate of 36.4 per 100,000. Non–Hispanic whites had a 1.2 times increase in homicide rates from 1970 to 1993 (from 5.0 to 5.9 per 100,000). Hispanic homicide rates rose 2.5 times (from 7.7 to 19.4 per 100,000), and homicide rates for Asians and others increased 1.7 times (from 4.5 to 7.6 per 100,000) from the 1970 rate during the same period. Thus, the greatest change in homicide rates by ethnicity is in two traditionally understudied groups, Hispanics and Asians.

The greatest increase in homicide rates was not for a certain sex or a specific ethnic group but for youth. Homicide rates for 15- to 19-year-olds increased 4.0-fold from 8.4 to 33.7 per 100,000 from 1970 to 1993 (Figure 3). The 5- to 14-year-old group had the second largest increase—3.2 times from 0.76 to 2.4 per 100,000—followed by 20- to 24-year-olds with a 2.6 times increase of 13.7 to 35.3 per 100,000. While the youth homicide rate climbed, the risk remained relatively stable or dropped for other age groups.

Changing patterns of relative risk are documented in Table 1. Whereas men consistently had significantly

higher homicide rates than women, their risk relative to women increased from 3.27 in 1970 to 1974 to 4.70 in 1990 to 1993. African Americans and Hispanics are at a substantially higher risk than non–Hispanic whites. Moreover, the differential increased over time, ending with a 9.00-fold risk for African Americans and a 3.26-fold risk for Hispanics in 1990 to 1993. Asians and others had lower relative risks during the early time periods (0.96, 0.71, 0.72, 0.86), indicating a protective factor until 1990 to 1993, when the relative risk changed direction and rose to 1.17, a statistically significant difference.

A pronounced change is noted for the 15- to 19-year age group. From 1970 to 1984, the risk of homicide for 15- to 19-year-olds was not significantly different from that for 35- to 44-year-olds. In the latter half of the 1980s, their relative risk increased substantially to a 2.26-fold risk in 1990 to 1993. Across each of the five time periods, 20- to 24-year-olds had the highest risk, and 5- to 14-year-olds had the lowest risk relative to the 35- to 44-year age group. The 20- to 24-year and 25- to 34-year age groups have consistently high relative risks for homicide, ending with a 2.41- and 1.50-fold risk of homicide, respectively, in 1990 to 1993. Persons younger than 15 years and older than 44 years were consistently at a lower risk of homicide than 35- to 44-year-olds.

For persons aged 25 and older during 1989 to 1993 (the years for which education level information is available), high school dropouts had a 1.63 (95% CI = 1.46, 1.83) times greater risk than high school graduates of being a homicide victim (data not tabled). Those with an eighth grade education or less did not differ significantly from those with a high school diploma (RR = 1.07; 95% CI = 0.95, 1.20). In comparison, persons with some college or who are college graduates have a substantially lower risk (RR = 0.44, 95% CI = 0.39, 0.50; and, RR = 0.23, 95% CI = 0.19, 0.27, respectively) of being a homicide victim.

As shown in Figure 1, the firearm homicide rate parallels the overall homicide rate, which can be explained by the large proportion of homicides involving firearms (see Figure 4). Firearms and explosives consistently accounted for about 60% of all homicides from 1970 until the mid–1980s, when the percentage began to climb. The percentage of homicides due to cuttings and stabbings dropped from 20% to 11%, and other methods have dropped from 24% to 14% of all homicides. In 1993, firearms and explosives accounted for 75% of all homicides.

Temporal variations (data not tabled) indicate that most homicides occur in the summer months (July through September), with the most homicides occurring in August. The average annual percentage of homicides adjusted by month varied from a low of 8.2% in February to a high of 8.9% in July and 9.1% in August. No significant seasonal differences were detected across the time periods, aside from the overall increase in the number of homicides each year.

Discussion

California data from 1970 to 1993 document a growing disparity in traditional patterns of homicide risk and a substantial shift in others. Homicide risk differences are increasing between men and women and between persons of color and non–Hispanic whites. Two tradi-

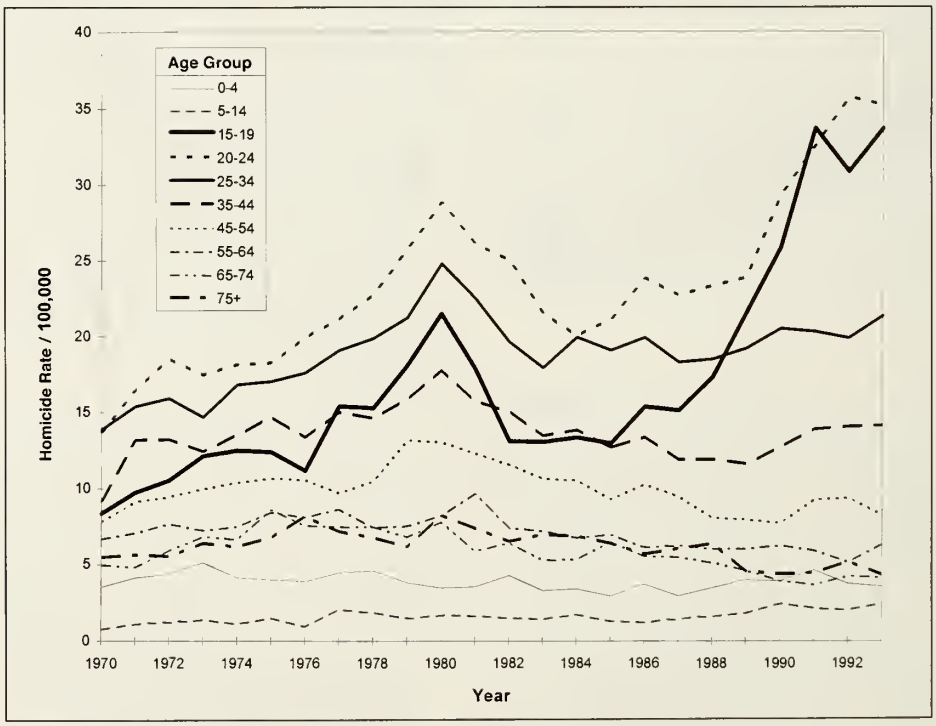

Figure 3.—The California homicide rates by age groups for 1970 to 1993 are shown.

TABLE 1.—*Relative Risks for California Homicides, 1970 to 1993**

Variable	*1970 to 1993*	*1970 to 1974*	*1975 to 1979*	*1980 to 1984*	*1985 to 1989*	*1990 to 1993*
Sex†						
Male	**3.83** (3.50, 4.19)	**3.28** (2.94, 3.65)	**3.51** (3.20, 3.85)	**3.87** (3.54, 4.23)	**3.67** (3.37, 4.00)	**4.71** (4.34, 5.10)
Race and Ethnicity‡						
African American	**7.26** (6.63, 7.94)	**7.33** (6.61, 8.12)	**6.17** (5.62, 6.77)	**6.42** (5.88, 7.01)	**7.64** (7.00, 8.34)	**9.01** (8.29, 9.79)
Hispanic	**2.55** (2.33, 2.79)	**1.96** (1.72, 2.23)	**2.43** (2.21, 2.67)	**2.48** (2.27, 2.70)	**2.27** (2.08, 2.48)	**3.26** (3.02, 3.53)
Asian and other	0.89 (0.73, 1.08)	0.96 (0.71, 1.30)	**0.71** (0.56, 0.92)	**0.72** (0.59, 0.89)	0.86 (0.72, 1.02)	**1.17** (1.02, 1.36)
Age, yr§						
0 to 4	**0.28** (0.22, 0.36)	**0.35** (0.27, 0.45)	**0.28** (0.22, 0.37)	**0.24** (0.19, 0.31)	**0.28** (0.22, 0.36)	**0.29** (0.24, 0.36)
5 to 14	**0.12** (0.09, 0.15)	**0.09** (0.07, 0.13)	**0.11** (0.08, 0.14)	**0.11** (0.08, 0.14)	**0.12** (0.09, 0.16)	**0.17** (0.13, 0.20)
15 to 19	**1.26** (1.10, 1.45)	0.87 (0.73, 1.04)	0.98 (0.85, 1.14)	1.05 (0.91, 1.21)	**1.34** (1.17, 1.54)	**2.26** (2.03, 2.52)
20 to 24	**1.75** (1.55, 1.98)	**1.38** (1.18, 1.61)	**1.47** (1.29, 1.68)	**1.61** (1.42, 1.82)	**1.88** (1.66, 2.12)	**2.42** (2.18, 2.68)
25 to 34	**1.42** (1.27, 1.59)	**1.25** (1.08, 1.45)	**1.29** (1.14, 1.47)	**1.39** (1.24, 1.55)	**1.55** (1.39, 1.73)	**1.50** (1.36, 1.64)
45 to 54	**0.73** (0.62, 0.85)	**0.76** (0.64, 0.91)	**0.740** (0.63, 0.87)	**0.77** (0.66, 0.89)	**0.73** (0.63, 0.86)	**0.63** (0.55, 0.73)
55 to 64	**0.52** (0.43, 0.63)	**0.59** (0.48, 0.73)	**0.54** (0.45, 0.65)	**0.52** (0.44, 0.62)	**0.51** (0.42, 0.62)	**0.43** (0.36, 0.52)
65 to 74	**0.42** (0.34, 0.53)	**0.48** (0.36, 0.62)	**0.51** (0.41, 0.64)	**0.41** (0.33, 0.51)	**0.44** (0.35, 0.55)	**0.29** (0.23, 0.37)
≥75	**0.45** (0.34, 0.58)	**0.48** (0.35, 0.66)	**0.48** (0.36, 0.62)	**0.48** (0.37, 0.61)	**0.47** (0.37, 0.61)	**0.34** (0.26, 0.44)

*Relative risks in bold-faced type are statistically significant at $P < .05$.
†Referent = female.
‡Referent = non-Hispanic white.
§Referent = 35- to 44-year olds.

tionally understudied population groups illustrate this trend well: Hispanics are at a consistently higher risk of homicide than non–Hispanic whites, whereas Asians and others were at a lower or similar risk until the 1990s, when their risk of homicide became significantly greater than that of non–Hispanic whites. African Americans are at an extremely high risk of homicide, a fact that has been widely documented and is corroborated herein. Thus, minority group status is associated with higher homicide rates, albeit not uniformly higher.

Young people are at a dramatically increasing risk of homicide. If existing trends continue, 15- to 19-year-olds will soon overtake 20- to 24-year-olds as the leading category in age-specific homicide rates. This is due, in no small part, to the fact that the homicide rate for 15- to 19-year-olds has more than quadrupled since 1970. Moreover, the homicide rate for persons aged 45 or older has remained stable or decreased. Thus, there is a pronounced trend toward younger victims of homicide.

High school dropouts are at the highest risk of homicide among all education groups. Persons with eight or fewer years of schooling are at a risk similar to that of high school graduates. By contrast, persons with some college or a college degree are at a substantially lower risk of homicide. Given that the education level was added recently to death certificate forms, the association between educational level and homicide risk is just beginning to be explored.[21]

Firearms play a central role in homicide; three of every four homicides in California in 1993 were committed with a firearm. Firearm homicide risk is even higher for youth: in the same year, 90% of the murdered 15- to 19-year-olds in California were killed with a gun. The increase in the number of firearm homicides has been related to an increase in firearm sales,[12] and keeping a gun in the home has been associated with an

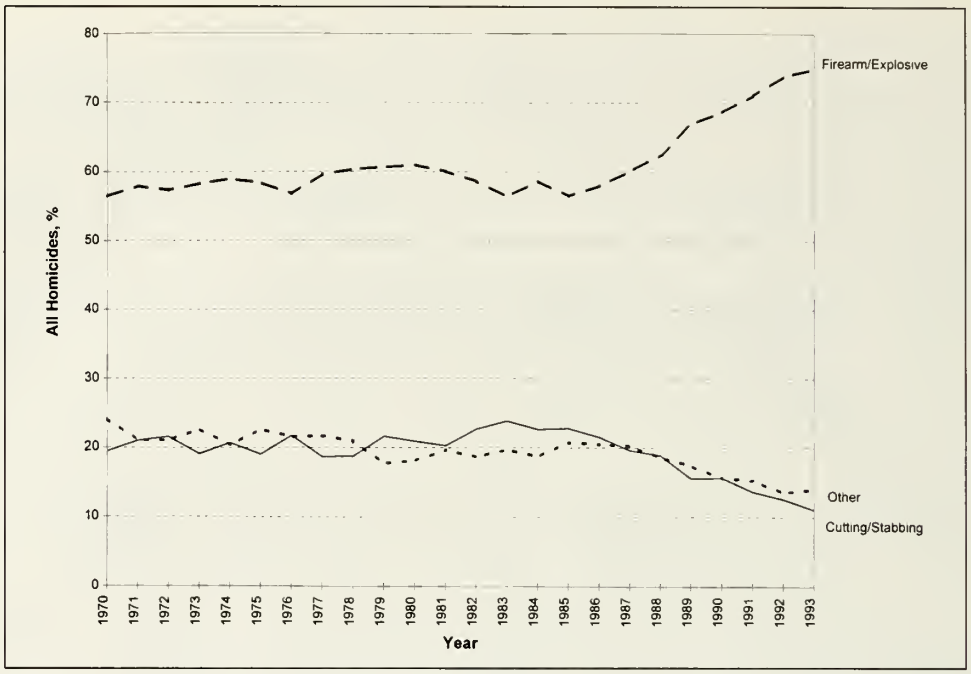

Figure 4.—The graph shows percentages of the methods of homicide—firearms or explosives, cutting or stabbing, or other—for 1970 to 1993.

increased risk of in-home homicide.[10] This is a disturbing outcome of the ease of obtaining a firearm in the United States, where "buying a handgun is as easy as buying a toothbrush."[22 (p1375)] Firearm deaths currently are the leading cause of injury death in California, surpassing even motor vehicle crashes; this change is mostly a result of an increase in the number of firearm deaths rather than a decrease in motor vehicle fatalities.[23]

A few cautions about these data should be noted. Because of the unique minority population distribution of California and the traditionally more violent aspect of the western United States,[15] these results may not generalize to other states or to the nation. Second, education data are relevant for persons aged 25 or older; therefore, associations between education and homicide risk are not valid for the bulk of homicide victims—15- to 24-year-olds—who are excluded from education analyses. Third, although we expect the numbers to be low, there may be some misclassification of Hispanics using the Spanish surname list when non–Hispanic women change their last names when they marry Hispanic men. Fourth, the Asian and other group contains Native Americans who have extremely high homicide rates,[24] which may strongly influence the overall Asian-and-other homicide rate. Last, homicide rates may be affected by the substantial increase in California's foreign-born population in the 1980s, a group that appears to be at a higher risk of homicide.[25]

Conclusion

Homicide is a growing problem among the populations traditionally served by public health agencies. Persons of color are at a substantially higher risk than non–Hispanic whites, and the differences between the groups are growing. Of particular concern is the rapidly escalating homicide risk for 15- to 19-year-olds and an accompanying increase among 20- to 24-year-olds. Furthermore, using recently available education data, these findings indicate that high school dropouts have the highest homicide risk of all educational groups. And, relative to that of women, men's risk of homicide is growing. In essence, even as we assess the role of previously undocumented factors such as education, long-established discrepancies in homicide risk are expanding.

Law enforcement efforts are crucial but singularly insufficient in reducing violence perpetration and victimization. Although the Centers for Disease Control and Prevention has exercised considerable leadership in the field, many state and local health departments still do not define violence and injury prevention as part of their mission. Public health departments need to develop the capacity to be an effective partner in collaborative interagency efforts to meet the thriving public health challenge of homicide.

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Epidemic *Salmonella enteritidis* Infection in Los Angeles County, California

The Predominance of Phage Type 4

DOUGLAS J. PASSARO, MD, *Berkeley, California;* ROSHAN REPORTER, MD, LAURENE MASCOLA, MD, *and* LIGA KILMAN, BSc, *Los Angeles, California;* GEORGE B. MALCOLM, BSc, *and* HENRY ROLKA, BSc, *Atlanta, Georgia; and* S. BENSON WERNER, MD, *and* DUC J. VUGIA, MD, MPH, *Berkeley, California*

Between April and July 1994, 501 cases of *Salmonella enteritidis* infection were reported in Los Angeles County, California, nearly 5 times the number reported between April and July 1993; of these, 422 (84%) were sporadic (not related to known outbreaks). A case-control study was done to determine risk factors for sporadic illness; the distribution of *S enteritidis* phage types was evaluated. Case-patients (n = 58) were county residents older than 1 year with culture-confirmed *S enteritidis* infection in August 1994. One to two acquaintance controls (n = 98) were matched to each case by age, sex, and race. Two risk factors—eating raw or undercooked eggs (matched odds ratio [MOR] = 6.6; 95% confidence interval [CI] = 1.9, 23.0) and eating in restaurants (MOR = 4.9; 95% CI = 1.2, 19.4) in the 3 days before the onset of illness—remained significant in the conditional logistic regression model. Of 16 randomly selected *S enteritidis* case-isolates, 15 (94%) were phage type 4. The reasons for the regional predominance of phage type 4, an *S enteritidis* subtype recently associated with large and destructive increases in salmonellosis among poultry and humans in Britain and much of Europe, are unclear. To minimize human *S enteritidis* infection, food service workers need frequent training in the proper handling of raw foods, eggs should be kept refrigerated during distribution and storage, and eggs should be cooked until the yolk is firm, particularly for persons at the greatest risk for serious illness: pregnant women, elderly persons, and those with compromised immune systems. Clinicians should obtain stool specimens for culture from patients who present with diarrhea and fever or bloody diarrhea or who are possibly part of an outbreak.

(Passaro DJ, Reporter R, Mascola L, et al: Epidemic *Salmonella enteritidis* infection in Los Angeles County, California—The predominance of phage type 4. West J Med 1996; 165:126-130)

Food-borne illness due to *Salmonella enteritidis* usually presents as a self-limited diarrhea with abdominal cramping, fever, and occasional vomiting. Pregnant women, elderly persons, and those with immunocompromise are at an increased risk for the development of invasive disease. Human *S enteritidis* infection has become an increasingly important public health problem since the early 1980s.[1,2] Before then, *S enteritidis* was an uncommonly reported *Salmonella* serotype globally. In the past 15 years, however, rates of illness due to this serotype have increased by fivefold to tenfold and more in the United Kingdom and in parts of Europe, Africa, and South America.[1,3,4] In the United States, the incidence of reported human *S enteritidis* infection has been highest in New England and the mid–Atlantic region.[3]

In Los Angeles County, California, 501 cases of *S enteritidis* infection were reported during the period April through July 1994, nearly five times the number of cases reported in the same four months of 1993 and more than twice the yearly average for 1990 to 1993 (Figure 1). Of these 501 cases, 422 (84%) were sporadic (unrelated to known outbreaks). This upsurge involved much of southern California: the number of cases tripled in nine southern California counties, from 261 in April through July 1993 to 799 in April through July 1994. In contrast, northern California counties experienced no overall increase during this period.

Of ten randomly selected Los Angeles County *S enteritidis* isolates collected in April 1994, nine (90%) were phage type 4. *Salmonella enteritidis* phage type 4 was a strain rarely isolated in the United States before 1990, and the first documented *S enteritidis* phage type 4–associated food-borne outbreak in this country was not reported until April 1993, in El Paso, Texas.[5] In May

From the California Department of Health Services, Berkeley (Drs Passaro, Werner, and Vugia); the Los Angeles County Department of Health Services (Drs Reporter and Mascola and Ms Kilman), Los Angeles, California; and the Centers for Disease Control and Prevention (Dr Passaro and Messrs Malcolm and Rolka), Atlanta, Georgia.

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Reprint requests to Douglas J. Passaro, MD, Disease Investigation and Surveillance Branch, Division of Communicable Disease Control, California Dept of Health Services, 2151 Berkeley Way, Berkeley, CA 94501.

ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control and Prevention
CI = confidence interval
DHS = Department of Health Services
MOR = matched odds ratio
USDA = United States Department of Agriculture

1994, eggs and hens in a large southern California egg ranch were found to be contaminated with *S enteritidis* phage type 4, the first time this strain had been documented in US poultry.[6]

In August 1994, the Los Angeles County Department of Health Services (DHS) and the California DHS undertook an investigation to identify possible risk factors for sporadic illness due to *S enteritidis* and to evaluate the distribution of *S enteritidis* phage types in this epidemic.

Cases and Methods

A matched case-control design was used to identify possible risk factors (foods and behaviors) associated with sporadic *S enteritidis* infection. A case was defined as an illness associated with culture-confirmed *S enteritidis* identified either in stool or blood specimens collected during August 1994 from a Los Angeles County resident older than 1 year. Only one case was included from each known outbreak or household cluster during the study period. Persons whose date of illness onset was not well defined due to the presence of chronic diarrhea—defined as more than 1 loose or watery stool daily for longer than a month—were excluded from the study. Also excluded were persons submitting specimens for "clearance" culture to return to work. Each case-patient provided one to two acquaintance controls, matched by age group (±1 year for case-patients <7 years old, ±3 years for case-patients 7 to 12 years old, ±5 years for case-patients 13 to 64 years old, and ±15 years for case-patients >64 years). Controls for case-patients older than 12 years were also matched for sex and race.

A questionnaire was administered by telephone to each study participant or, if younger than 12 years, to his or her parent. The questionnaire included questions about 135 specific food items eaten in the three days before the onset of illness and about activities (for instance, camping, drinking open-source water, or traveling outside Los Angeles County) in the week before onset (a longer time period was used for assessing behavioral exposures because of the ongoing or intermittent nature of many of those exposures). Control participants were asked about the same exposures during the same reference period as the case-patients with whom they were matched. If recall was a problem, the controls were instead asked about the same three days of the week from the week following the reference period for food exposures and the entire following week for other activities. If a participant was uncertain whether a given exposure occurred, a "not exposed" response was coded.

An "egg dish" was defined as scrambled, boiled, fried, poached, or uncooked eggs, omelets, quiches, eggs Benedict, or other foods that contain eggs as a primary ingredient. "Undercooked egg" referred to an egg that was cooked so that any of the yolk remained liquid, regardless of the preparation method. "Seafood" included shrimp, lobster, crawfish, clams, oysters, mussels, squid, and octopus, but not finned fish. "Soft cheese" included rancher's cheese (*queso ranchero*), Brie, or other spreadable cheese, but not cream cheese or cottage cheese. A "restaurant" was any commercial food preparation establishment, including fast-food outlets and street vendors.

All clinical and reference laboratories in Los Angeles County forwarded *Salmonella* group D isolates to the county's Public Health Laboratory or the California DHS Microbial Diseases Laboratory for serotype confirmation and identification. A random sample of 16 (28%) of 58 case-isolates from August 1994 was sent to the

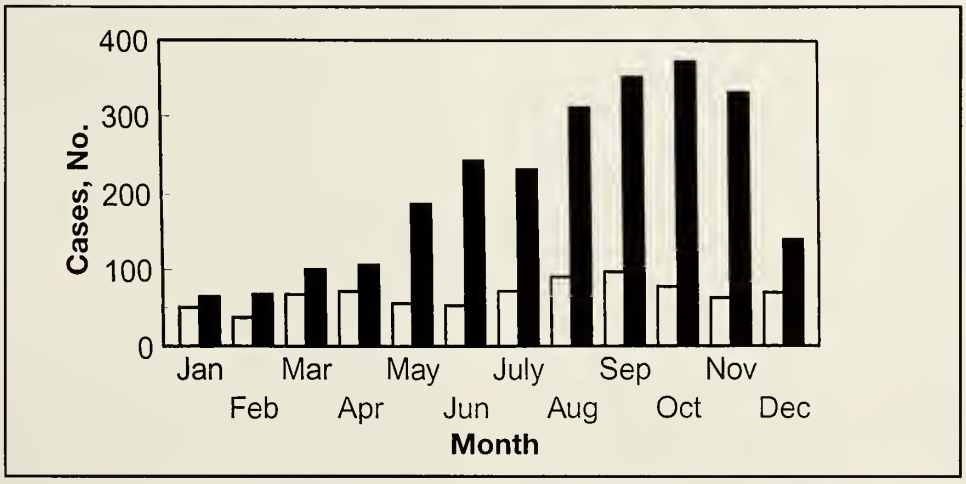

Figure 1.—California State Department of Health Laboratory–confirmed isolates of *Salmonella enteritidis* are shown by month. ❑ = 1990 to 1993 cases (mean), ■ = 1994 cases

TABLE 1.—*Association Between Sporadic Illnes Due to* Salmonella enteritidis *and Selected Foods and Activities Before Onset of Illness, Los Angeles County, August 1994 (matched bivariate analyses only)*

Food* or Activity†	Exposed Coses, (n = 58), No. (%)		Exposed Controls (n = 98), No. (%)		Motched Odds Rotio (95% Confidence Intervol)
Egg dishes	37	(64)	45	(46)	3.0 (1.2, 7.9)
Raw or undercooked egg dishes	20	(34)	11	(11)	10.0 (2.5, 46.4)
Raw eggs	6	(10)	1	(1)	11.0 (1.2, 473.1)
Seafood	8	(14)	4	(4)	4.0 (1.0, 26.5)
Soft cheese	8	(14)	5	(5.1)	2.6 (0.7, 13.1)
Chicken	43	(74)	54	(55)	1.5 (0.7, 3.5)
Hamburger	20	(34)	49	(50)	0.3 (0.2, 1.1)
Turkey	6	(10)	27	(28)	0.2 (0.1, 0.8)
Apples	9	(16)	34	(35)	0.1 (0.1, 0.6)
Eating in restaurants	51	(88)	68	(69)	5.6 (1.6, 29.1)
Working in restaurants	1	(2)	0	(0)	Undefined
Travel out of county	11	(19)	9	(9)	3.6 (1.0, 12.7)
Exposure to pets	34	(59)	52	(53)	1.3 (0.6, 2.6)
Drinking from open water source	2	(3)	0	(0)	Undefined

* During the 3 days before the onset of illness.
† During the 7 days before the onset of illness.

Centers for Disease Control and Prevention (CDC) for phage typing.[7]

Crude comparative (bivariate) analysis was done by applying Mantel-Haenszel matched χ^2 analysis to dichotomous variables. Adjusted (multivariable) analysis was done using backward-elimination conditional logistic regression, which was applied to all risk factors associated with a P value of less than .20 in the crude comparative analysis.

Results

Of 143 Los Angeles County residents in whom *Salmonella enteritidis* was identified from August 1 through August 31, 1994, 13 persons were determined to have *S enteritidis* infection related to a known outbreak, 7 were younger than 1 year at the time of specimen collection, and 3 were household contacts of persons with documented *S enteritidis* infection. Of the 120 persons who otherwise met the case definition, 32 could not be located despite numerous attempts, and 5 refused or were too sick to provide a food history. Of the remaining 83 persons, 25 did not provide appropriate controls. The 58 remaining persons provided 98 matched controls: 40 provided two matched controls, and 18 provided one matched control. The median age of case-patients was 25 years (range, 1 to 93 years). Males and females were equally represented (29 each). The racial or ethnic distribution of the 58 cases was 34 (59%) non–Hispanic white, 12 (21%) Hispanic white, 8 (14%) African American, and 4 (7%) Asian or Pacific Islander.

Foods eaten more commonly by case-patients than by controls included egg dishes and seafood (Table 1). Notably, of the 37 case-patients who ate eggs, 20 (54%) reported eating them either undercooked or raw.

Behaviors that were significantly more common among case-patients than among controls included eating in any restaurant during the three days before becoming ill and traveling outside of Los Angeles County in the week before the illness (see Table 1). Of 20 study participants who traveled, 18 (90%) also ate in restaurants. No individual restaurants were associated with sporadic *S enteritidis* infection.

In the conditional logistic regression model, eating in restaurants, eating egg dishes, eating seafood, and eating soft cheese in the three days before illness were associated with *S enteritidis* infection. Because *Salmonella* species in food is destroyed by thorough heating, we categorized exposure to "eggs dishes" by how completely they had been cooked before being eaten. When the multivariable analysis was repeated using the subgroups "raw or undercooked eggs" and "well-cooked eggs" in place of "egg dishes (all)," only two exposures—eating raw or undercooked eggs (matched odds ratio [MOR] = 6.6; 95% confidence interval [CI] =1.9, 23.0) and eating in restaurants (MOR = 4.9; 95% CI = 1.2, 19.4)—were associated with an increased risk of *S enteritidis* infection.

One case-isolate was from blood; all other isolates were from stool. Of 16 case-isolates from August 1994 sent to the CDC for phage typing, 15 (94%) were phage type 4, and 1 was phage type 1. Therefore, a total of 24 (95%) of 26 *S enteritidis* isolates from Los Angeles County phage typed by the CDC in 1994 were phage type 4.

Discussion

Eating in restaurants and eating eggs (particularly undercooked or raw eggs) were significant risk factors for sporadic *S enteritidis* infection in Los Angeles County in August 1994 and may be major contributors to the upsurge of *S enteritidis* infections throughout southern California. California now clearly shares the problem of *S enteritidis* as an emerging infection with

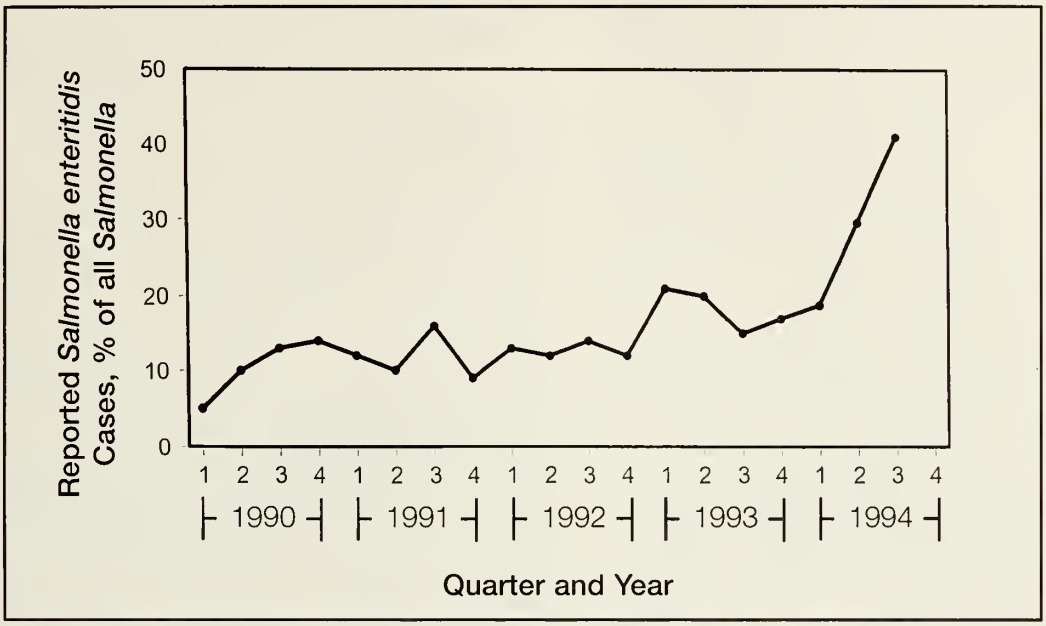

Figure 2.—Cases of *Salmonella enteritidis* as a percentage of all California *Salmonella* cases are shown, by quarter, for 1990 to 1994.

the eastern United States, although it is not clear why northern California has been spared to date.

This upsurge is unlikely to be an artifact of increased reporting. Although the total number of cases of human salmonellosis in California has risen only slightly in the past five years, *S enteritidis* accounts for an increasingly large proportion of these cases: in 1994, *S enteritidis* accounted for 35% of isolates statewide, compared with 18% in 1993 and only 12% in 1990 through 1992 (Figure 2).

The results of this study are consistent with findings of one British and two US studies that reported that eggs are an important risk factor for sporadic *S enteritidis* infection.[8-10] Similarly, eggs have been the most commonly implicated food item in *S enteritidis* outbreaks in the United States (1985 to 1993) for which a source has been identified (193 [86%] of 223 outbreaks).[1]

Eating in restaurants was the other important risk factor for *S enteritidis* infection, and this, too, has previously been noted[9]; undercooked eggs may be an unrecognized ingredient in many dishes, and imperfect food service sanitation practices may result in the cross-contamination or undercooking of foods.[11]

This study has several limitations. One was the possibility of bias in the selection of case-patients: a substantial proportion (31%) of residents who met the case definition were not included in our study because we could not contact them by telephone or they refused to be interviewed. Another limitation is that our study sample does not accurately reflect the racial or ethnic distribution of Los Angeles County. In particular, persons of Hispanic descent were underrepresented: whereas 40% of the county's population is Hispanic, Hispanics comprised only 21% of our case-patients. This occurred largely because Hispanic case-patients were disproportionately unable or unwilling to give out the telephone numbers of possible controls to investigators. Of 32 possible Hispanic case-patients, 20 (63%) were excluded from the study for failing to provide appropriate controls, the highest percentage of any racial or ethnic group.

In May 1994, chicken flocks were found to be infected with *S enteritidis* phage type 4 at an egg ranch in southern California, and eggs from those flocks were diverted to pasteurization. Preventing unpasteurized eggs from these flocks from reaching the consumer market, however, has not prevented the upsurge of *S enteritidis* infection in southern California. This suggests that other egg and nonegg sources of *S enteritidis* continue to contribute to the epidemic of salmonellosis in southern California. Although *S enteritidis* phage type 4 is the epidemic strain of *S enteritidis* in much of the world, including the United Kingdom, western Europe, and parts of South America,[3,5] this is the first time that this strain has been found to predominate among human *S enteritidis* isolates in a region of the United States, and it is the first time that it has been found in a US producer flock. The biologic mechanisms enabling *S enteritidis* phage type 4 to become a predominant phage type causing human illness remain unknown.

A trace-back of eggs associated with human *S enteritidis* infection, an important step in identifying the source of this epidemic, could not be performed. In California, as elsewhere in the United States, eggs from various sources are typically mixed by distributors before shipping to retail outlets. Before October 1, 1995, when investigating an outbreak or cluster of *S enteritidis* cases thought to be caused by eggs, the US Department of Agriculture (USDA) attempted to do a trace-back to

the egg ranch(es) of origin. If the trace-back identified two or more ranches as the possible sources, no microbiologic testing of the flock or premise was done. This policy made it difficult to identify the ultimate sources of sporadic egg-associated *S enteritidis* cases. Moreover, starting October 1, 1995, even *S enteritidis* outbreaks with a likely egg source may not be traced back; in the most recent federal budget, the USDA has been prohibited from spending funds on *S enteritidis* activities such as trace-backs and on-ranch testing.

Despite the fact that no trace-back was done as a result of this investigation, the documentation of an *S enteritidis* epidemic in southern California, the recent finding of *S enteritidis* phage type 4 in a local egg ranch concurrent with the epidemic, and the association of Los Angeles County *S enteritidis* cases with egg consumption suggest that this major public health problem may persist or worsen, as experience with *S enteritidis* in the northeastern United States has shown. Indeed, the *S enteritidis* epidemic in California has continued unchecked since this case-control investigation was done: in 1995, 2,495 cases of *S enteritidis* were reported to California DHS, a 300% increase compared with the yearly averages for 1990 to 1993. Furthermore, although no association with egg consumption was shown, ten Los Angeles County residents died after *S enteritidis* infection in 1995, the same number that died with the infection in 1994.

It is disturbing that a high percentage of persons who ate eggs reported eating them raw or undercooked; local, state, and federal agencies, as well as the egg industry, have repeatedly tried to alert the public about the risk of eating undercooked eggs. The USDA and the egg industry also advise consumers to cook their eggs thoroughly. Our findings suggest that the message is not reaching the public or that it is unwilling to change its eating habits.

Unlike most other *Salmonella* serotypes, *S enteritidis* can invade the ovary and oviduct of poultry and lead to vertical transmission: *S enteritidis* that has infected hens by oral, intravenous, or cloacal routes has resulted in the transovarian transmission of *S enteritidis* to eggs and chicks.[12–14] This has profound implications for both the poultry industry and the public: it means that because *S enteritidis* cannot be eliminated from egg-laying flocks using current technology, *S enteritidis*–infected eggs could reach the consumer market despite exemplary sanitation practices from the ranch onward.

Several recommendations can be made to minimize the public health risks associated with *S enteritidis* infection. Persons at greatest risk for serious illness, such as pregnant women and elderly and immunocompromised persons, should be reminded of the importance of properly cooking eggs (until the yolk is firm) to minimize the risk of contracting salmonellosis. Pasteurized eggs should be made widely available to individual consumers and should be used instead of pooled shell eggs in health care institutions and, when possible, in restaurants. Restaurants and institutions should review their recipes containing shell eggs and modify them, where appropriate, to ensure that eggs are adequately cooked. Eggs should be refrigerated during the entire ranch-to-consumer distribution process to assure egg quality and to minimize bacterial counts in previously infected eggs; this has been successfully mandated in California by amendments to the California Uniform Retail Food Facilities Law that were signed January 1, 1996. Together, egg industry and public health officials should develop a system to determine the sources of eggs that are found to be implicated in salmonellosis outbreaks or that are documented to be contaminated. Food workers should receive frequent training in hand-washing techniques and in the proper handling and preparation of all raw food products of animal origin, including shell eggs. Studies should be done to determine the relative virulence of *S enteritidis* phage type 4 for humans and to determine the current prevalence of *S enteritidis* in shell eggs sold to consumers. Clinicians should be alert to the problem of *S enteritidis* infection and should submit stool specimens for culture when their patients present with diarrhea and fever or bloody diarrhea or are suspected to be part of an outbreak.

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Conferences and Reviews

Predictors of Thyroid Tumor Aggressiveness

ORLO H. CLARK, MD, *San Francisco, California*

This article is based on a lecture given at the American Thyroid Association as the Paul Starr Award, Tampa, Florida, November 1993.

Thyroid cancers are classified as papillary, follicular (including Hürthle cell), medullary, and anaplastic. Papillary cancers account for about 82% of all thyroid cancers, follicular about 8%, medullary about 6%, Hürthle cell 3%, and anaplastic 1%. The prognosis of patients with papillary thyroid cancer is usually favorable, whereas most patients with anaplastic cancer die within 6 months. The behavior of papillary thyroid cancer can be predicted by patient age, sex, tumor size, local invasion, angioinvasion, lymph node metastases, distant metastases, as well as tumor differentiation and ability to take up radioactive iodine. Thus, older male patients with larger or invasive tumors, with angioinvasion, lymph node or distant metastases, and with tumors that do not take up radioactive iodine or cannot be completely surgically resected have a worse prognosis. Anaploid tumors, tumors with a low adenylate cyclase response to thyroid-stimulating hormone tumors, tumors that are *ras*- and *gsp*-positive, and tumors that are p21-positive and p53-positive also appear to behave in a more aggressive manner. In contrast, lymphocytic thyroiditis associated with papillary thyroid cancer predicts fewer recurrences and an improved survival.

The treatment of patients with papillary thyroid cancer is controversial primarily because most patients do well with relatively minimal therapy, and there are no prospective studies concerning the merits of various treatments. Much of the controversy relates to the safety of thyroidectomy versus other procedures and, to a lesser extent, when to do a central or modified radical neck dissection. The rate of recurrence is lower, and the death rate may also be lower when patients are treated initially by total thyroidectomy. The rationale for total thyroidectomy is that it enables one to use radioactive iodine to detect and treat local and distant metastases, and it makes serum thyroglobulin determination more sensitive for detecting persistent disease. Total thyroidectomy should be associated with a permanent complication rate of less than 2%. Thyroid-stimulating hormone suppression therapy is recommended by most experts for patients with differentiated thyroid cancer and supported by most clinical and laboratory studies. Central and lateral node selection is recommended for patients with palpable lymphadenopathy.

(Clark OH: Predictors of thyroid tumor aggressiveness. West J Med 1996; 165:131-138)

Thyroid cancer is a fascinating tumor because of its variable and generally favorable course. Many more people have thyroid cancer than are aware of it, and most of them die with their tumor rather than of their tumor. For example, as many as 13% of persons in the United States have thyroid cancer at postmortem examination, and yet clinical thyroid cancer develops in only about 40 per million persons, and only about 6 per million (15%) die of it.[1(p123)] Thyroid cancer is, however, the most lethal endocrine neoplasm, excluding that of the ovary, and accounts for about 1% of all cancer deaths.[2]

The optimal treatment of patients with thyroid cancer is a topic of considerable controversy, and no prospective randomized trials comparing the various means of surgical with other treatments have been done. Most studies document that more extensive initial treatment reduces the recurrence and death rates from thyroid cancer, but more extensive treatment is also generally associated with more complications.[2-6]* Obviously, if the behavior of a particular tumor can be predicted, the use of various treatments such as total thyroidectomy, radioactive iodine ablation, thyroid-stimulating hormone (TSH) suppressive therapy, and external radiation treatment can be selective.

Thyroid cancers are classified as papillary, follicular, medullary, and undifferentiated or anaplastic. Mixed papillary-follicular cancers and follicular variants of

*See also the editorial by S. K. Grebe, MD, and I. D. Hay, MB, PhD, "Prognostic Factors and Management in Thyroid Cancer—Consensus or Controversy?" on pages 156–157 of this issue.

From the Department of Surgery, University of California, San Francisco (UCSF), School of Medicine and Mount Zion Medical Center, San Francisco.
Reprint requests to Orlo H. Clark, MD, Dept of Surgery, UCSF/Mout Zion Medical Center, 1600 Divisadero St, San Francisco, CA 94115.

ABBREVIATIONS USED IN TEXT

AGES = age, grade, extent, and size
AMES = age, metastasis, extent, and size
EGF = epidermal growth factor
EORTC = European Organization for Research and Treatment of Cancer
TSH = thyroid-stimulating hormone

papillary cancers are classified as papillary thyroid cancer because they behave in a similar manner. Hürthle cell cancers are of follicular cell origin and are usually included with follicular cell cancers—"Hürthle cell variant of a follicular cancer."[7] Hürthle cell cancers differ from follicular thyroid cancer because Hürthle cell cancers are often multifocal in the thyroid, are usually associated with regional lymph node metastases, and in general, do not take up radioactive iodine. Follicular thyroid cancers, in contrast, are usually solitary, involve only the regional nodes in 10% of patients, and take up radioactive iodine in about two thirds of patients.[8,9]

Papillary thyroid cancers account for about 82% of all cases of thyroid cancer in iodine-sufficient areas. Follicular cancers account for about 8%, medullary thyroid cancers 6%, Hürthle cell cancers 3%, and anaplastic thyroid cancer 1%. Other rare tumors of the thyroid include lymphomas (usually B-cell type), squamous cell carcinomas, angiosarcomas, teratomas, liposarcomas, and leiomyosarcomas. Tumors may also metastasize to the thyroid gland, the most common being hypernephroma, breast cancer, lung cancer, and malignant melanoma. Fortunately, about 98% of thyroid cancers are differentiated tumors, and therefore, most patients have a good-to-excellent prognosis. Unfortunately, few patients with anaplastic, squamous cell, and angiosarcoma survive more than six months despite the use of surgical treatment, radiation therapy, or chemotherapy. Therefore, histologic examination is important in predicting the prognosis.[10,11] Patients with poorly differentiated cancers also have more aggressive tumors and a poorer prognosis than do patients with well-differentiated thyroid tumor.[12] Histologic grading using Broders' classification was a cause-specific important prognostic factor by both univariate and multivariate analyses.[13-15] A group of recognized pathologists from World Health Organization collaborating centers in 1988 concluded, however, that "[T]he value of histological grading of papillary carcinoma remains to be substantiated."[16] Despite this statement, histologic differentiation was reported to be an independently important factor concerning thyroid cancer-related deaths.[17,18] I certainly concur with this opinion.

Staging

Numerous classifications have been used to determine prognostic factors, including the following:

- The European Organization for Research and Treatment of Cancer (EORTC) prognostic index based on multivariate analysis and using a Weibull survival model[19];
- The AGES [age, grade, extent, and size] classification using the Cox model[20];
- The AMES [age, metastasis, extent, and size] classification[21]; and
- The International Union Against Cancer or TNM [tumor, node, metastasis] classification (Figure 1).[14]

DeGroot and co-workers have described a simple classification: class 1, intrathyroidal disease; class 2,

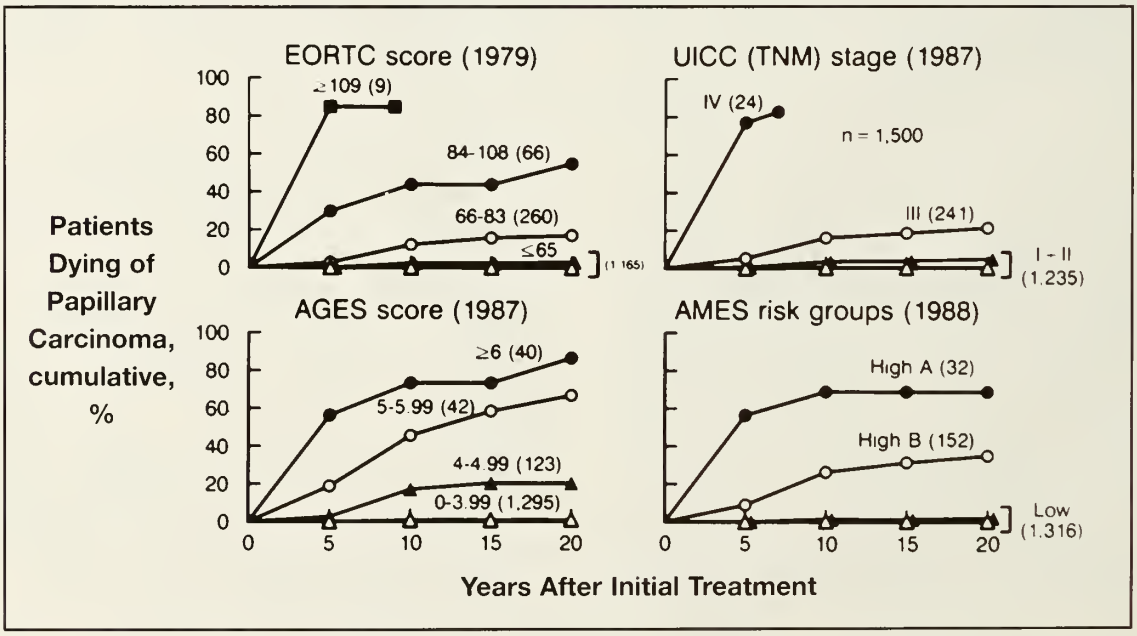

Figure 1.—Various staging indices are shown for patients with papillary thyroid cancer (from Hay,[13] with permission). AGES = age, grade, extent, and size; AMES = age, metastases, extent, and size; EORTC = European Organization for Research and Treatment of Cancer; TNM = tumor, node, metastasis; UICC = International Union Against Cancer.

TABLE 1.—*Prognostic Index System for Papillary Carcinoma**

Factor	*MACIS Score*
Age, years	
<39	3.1
≥40	0.08 × age
Diameter of primary	0.3 × cm
Incomplete resection	1
Extrathyroidal invasion	1
Distant metastases	3

MACIS = metastases, age, completion of resection, invasion, and size

*From Hay et al,[22] with permission.
†The MACIS scoring system is from the Mayo Clinic. Low risk ≤ 6, highest risk > 8.

regional lymph node metastasis; class 3, local invasion; and class 4, distant metastasis.[6] A newer classification has also been described by Hay and associates, with emphasis not only on age, size, and metastases, but also on the completeness of resection (Table 1).22 All of these classifications are helpful in predicting low and high risk. Unfortunately, some patients in the low-risk group still die of thyroid cancer, so better prognostic predictors are obviously necessary.

Virtually all studies document that young patients with thyroid cancer, such as men younger than 40 and women younger than 50, do better than older patients.[14] Patients with small tumors (<2 cm) do better than those with moderate-sized tumors (2 to 4 cm), and these patients do better than those with larger tumors (≥4 cm). Patients with locally invasive tumors and those with metastatic disease have a worse prognosis.14,21 Patients with tumors that cannot be resected have a poorer prognosis.[22] It should be noted, however, that the trachea can be resected with the preservation of a normal voice and that the esophageal wall can be resected with excellent results (Figure 2).

The site and number of metastases are also important. About 15% of children and 10% of adults will have pulmonary micrometastases at the time of the initial treatment.[23,24] Patients with pulmonary micrometastases have a considerably better survival rate than those with macrometastases, and these patients in turn have a better prognosis than those with skeletal metastases.[25]

We might question whether the AGES or other classifications are preoperative or postoperative classifications. Obviously, the age of a patient and the approximate size of the tumor can be determined preoperatively, and cytologic examination, as obtained by percutaneous aspiration biopsy, can usually determine the histologic type. Other proven risk factors such as invasion and distant metastases can often be determined only at or after surgical treatment. Other minor or major risk factors such as the presence of multifocal tumor,[26] lymph node involvement,[27,28] or focal areas of poorly or undifferentiated tumor are also best determined after examination of the entire specimen. Other predictors of aggressiveness include sex (women do somewhat better than men)[13,29,30]; ploidy (patients with aneuploid papillary, Hürthle cell, and medullary thyroid tumors do worse than those with diploid thyroid cancers)[31–34]; radioactive iodine uptake (patients whose tumors fail to take up radioactive iodine have a worse prognosis)[35,36]; adenylate cyclase response to TSH therapy (patients whose tumors have a low response do worse)[37]; epidermal growth factor (EGF) receptors (patients with higher EGF binding appear to do worse)[38]; oncogenes (patients with several oncogenes such as *ras* and *gsp* appear to do worse)[39]; and tumor suppressor genes (patients with p53, in general, appear to do worse).[40–42]

Tumor cell nuclear DNA content has been documented to be one of the best prognostic indicators of malignant potential,[13] and Bäckdahl and associates have said that the nuclear DNA content has a "predictive power significantly greater than that of all other prognostic factors combined."[31(p977)] Subsequent investigations have shown that the DNA ploidy pattern as determined by flow cytometry is an important and independent prognostic variable.[13,34] As shown in Figure 3, patients with an aneuploid DNA pattern have a worse prognosis than those with a tetraploid or diploid pattern. The DNA ploidy is a better prognostic factor for some tumors such

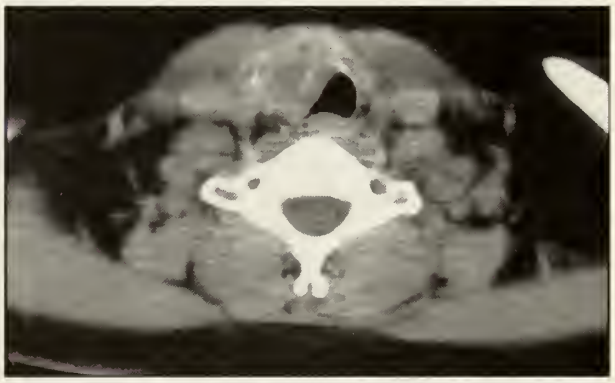

Figure 2.—A magnetic resonance imaging scan shows papillary thyroid cancer invading through tracheal wall.

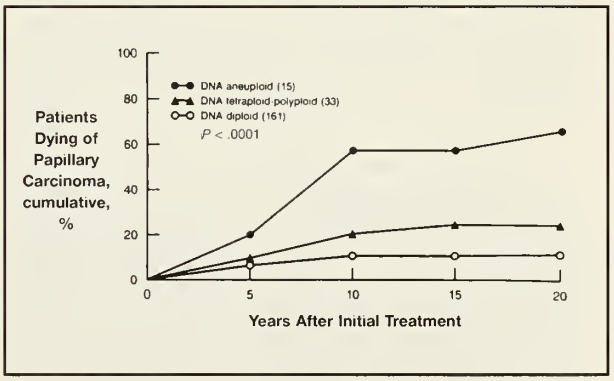

Figure 3.—The DNA ploidy pattern, prognosis, and cumulative mortality from papillary thyroid carcinoma are shown in 209 patients. Nuclear suspensions were obtained from paraffin-embedded archival tumor specimens (from Hay,[13] with permission). The numbers in parentheses indicate the number of patients.

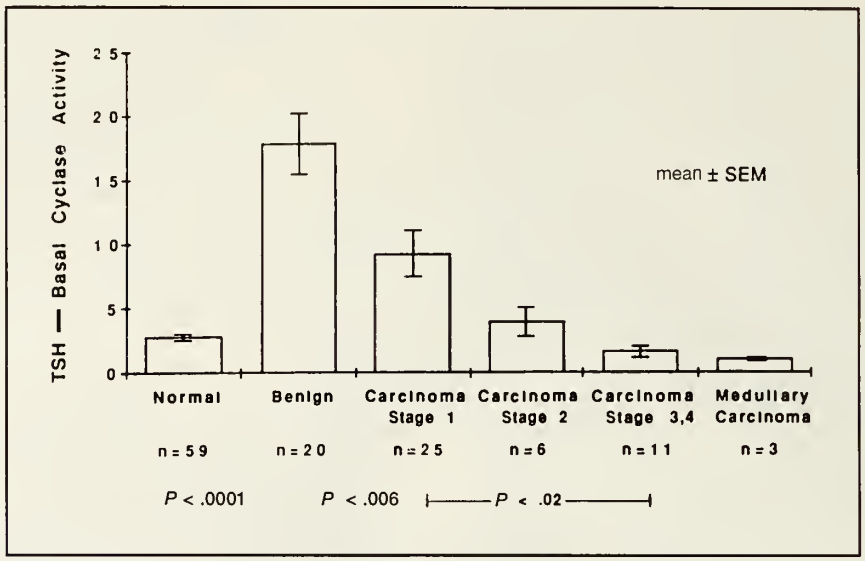

Figure 4.—The adenylate cyclase response to thyroid-stimulating hormone (TSH) therapy by tumor class is shown (from Siperstein et al,[37] with permission). SEM = standard error of the mean.

as papillary and Hürthle cell cancers than it is for others such as follicular cancer.[13,34,43] Ploidy is not useful for determining whether a particular thyroid tumor is benign or malignant.

About two thirds of all papillary and follicular thyroid cancers take up radioactive iodine, whereas few Hürthle cell, medullary, or anaplastic thyroid cancers take up radioactive iodine.[7,25] It is not surprising that patients whose thyroid cancers take up radioactive iodine have a better prognosis because such tumors are usually better differentiated and can sometimes be ablated with radioactive iodine.[3,35,36]

It has been documented that patients with tumors that are more extensive or disseminated have a lower adenylate cyclase response to TSH therapy (Figure 4).[37] Patients with tumors localized in the thyroid gland or nodal metastases had a ninefold to seventeenfold increase in adenylate cyclase activity, whereas those with more extensive tumors had only a twofold to threefold increase. Some of the decreased adenylate cyclase response in the more extensive or disseminated tumors was due to an increased basal adenylate cyclase activity, suggesting that such tumors are constitutively activated. In another study, two of three patients with constitutively activated adenylate cyclase and follicular thyroid carcinomas and one of three patients with a constitutively activated papillary thyroid cancer had a *gsp* (stimulating G protein) oncogene.[44] These oncogenes were initially identified in a "hot" thyroid nodule and subsequently in 5 of 13 (38%) autonomous nodules.[45,46] In another investigation, patients with both *ras* and *gsp* oncogenes appeared to have more aggressive tumors (Table 2).[39] Elsewhere it was found that *ras* mutations are present in about 40% of follicular thyroid cancers.[47] In addition, the overall prevalence of *ras* mutations was the same in 68 spontaneous and 12 radiation-associated thyroid tumors, although thyroid carcinomas in the radiated group had significantly more K-*ras* mutations (60% to 67%) ($P < .005$).[48] A history of irradiation increases the frequency of multifocal thyroid tumors, but probably does not influence tumor aggressiveness.[49] It has been documented that the *ras* oncogene product, p21, is only weakly expressed in normal thyroid tissue, but it is more strongly expressed in thyroid neoplasms.[50] In another study, p21 staining was positive in 35 of 51 (65%) thyroid neoplasms, and a significantly positive correlation was found between outcome and p21 tumor staining.[51] Overall, in patients with papillary and follicular thyroid cancers, 83% of those who died had thyroid cancers that stained positively, whereas staining was positive in 52% of the survivors ($P < .02$).

An oncogene (*ptc*) has been identified in papillary thyroid cancers.[52] This oncogene is a variant of the ret proto-oncogene. Subsequently the *ptc* oncogene was found on chromosome 10q11-12 in the same region as that for multiple endocrine neoplasm type 2A.[53] The *ptc* oncogene has tyrosine kinase activity. This signal transduction pathway has been reported to be involved in the

TABLE 2.—*Oncogene* gsp *and* ras *Mutations in Differentiated Thyroid Cancer**

Tumor Stage	*Patients, No.*	*Patients Positive, No. (%)* ras	gsp	ras *and/or* gsp
Unilocal intrathyroidal, T1-2, N0-1, M0	10	1	5	5 (50)
Multifocal and lymph node metastases, T3-4, N2-3, M0	13	3	7	8 (62)
Distant metastases, TX, NX, M1	9	5	6	8 (89)

*From Goretzki et al.[39]

TABLE 3.—*Effects of Prophylactic Neck Dissection on Recurrence and Survival**

Elective Neck Dissection	Patients No.	Later Active Disease, No. (%)	Dead of Disease, No. (%)
Yes	76	3 (4)	2 (3)
No	88	18 (20)	5 (6)
Total	164	21 (13)	7 (4)

*From Hunter et al.[19]

pathogenesis of papillary thyroid cancer.[53]

The p53 gene acts as a tumor suppressor gene or as a dominant transforming oncogene. Although only 1 of 130 thyroid tumors was initially found to have a p53 mutation,[54] mutations were recently identified in 6 of 7 undifferentiated thyroid carcinomas[40] and in thyroid cancer cell lines.[41] Subsequent studies using single-strand conformation polymorphism analysis of complementary DNA fragments amplified by reverse transcriptase polymerase chain reaction documented the presence of mutations in exons 5, 6, 7, and 8 of the p53 gene in 12 of 49 thyroid carcinomas, but in 0 of 8 benign thyroid tumors.[42] The presence of p53 mutations was not associated with tumor stage or histologic type. We have also recently identified p53 mutations in three of the four thyroid cancer cell lines that we have established in our laboratory. The documentation of various combinations of oncogenes and tumor suppressor genes will probably prove to be useful for predicting tumor behavior.

There has been confusion concerning whether the presence of metastatic thyroid cancer in cervical lymph nodes is a prognostic factor. Numerous studies have documented that about 80% of patients with papillary thyroid cancer have at least micrometastases in cervical lymph nodes.[27,55,56] Palpable lymph nodes, however, are found in about 15% of adults and in about 50% to 80% of children.[23]

It was initially suggested that the finding of clinically involved cervical lymph nodes was beneficial in patients with thyroid cancer.[57] This seemed surprising because the presence of nodal metastases is detrimental for all other cancers. Some investigators have reported that the presence of nodal metastases has no detrimental effect on survival.[13,58] Others have found that the presence of involved lymph nodes adversely influences tumor recurrence, especially in patients older than 40, but does not influence survival.[5] Today in the United States, patients with thyroid cancer are generally treated by therapeutic (palpable lymph node metastases present) rather than by elective (no palpable lymph node metastases present) modified neck dissection because in most patients with microscopic nodal metastases, clinically evident nodal metastases do not subsequently develop.[59] Hutter and co-workers, in their classic article concerning elective radical neck dissection for papillary thyroid cancer, concluded that "[W]e find no real evidence to support the philosophy of radical neck dissection for patients with papillary carcinoma of the thyroid who have no clinical evidence of cervical lymph node metastases."[59(p92)] This study is of interest, but on reanalyzing their data the above conclusion is questionable. In their retrospective review of 164 patients, 76 patients had an elective radical neck dissection and 88 patients did not. The mean age of the patients having elective dissection was 47.9 years, whereas the mean age of the patients not having an elective neck dissection was 37.4 years. As shown in Table 3, the recurrence rate was 4% in the 76 patients having prophylactic neck dissection and 20% in the 88 patients who did not. The death rate was 3% in patients having prophylactic neck dissections and 6% in those who did not. These findings are of even more interest because only 38 of the 76 patients (50%) having elective node dissection were found to have thyroid cancer in their cervical nodes. We also do not know how these patients were selected for prophylactic neck dissection, but we might guess that more patients at higher risk would have been treated prophylactically. Also of interest, as seen in Table 3, none of the patients who had a neck dissection had recurrence in their cervical nodes, although recurrent disease developed in the thyroid gland of two patients and in both the thyroid gland and at distant sites in one patient.[59]

These data document that neck dissection is effective in preventing recurrence in patients with occult thyroid cancer in the cervical nodes. It is also of interest, even though the groups are small, that there were fewer recurrences and fewer deaths in the group treated by prophylactic dissection. This is surprising because, as mentioned, the group treated prophylactically was an average of ten years older and would have been expected to have a worse prognosis.

It is certainly understandable why most surgeons at medical centers in Japan continue to do ipsilateral modified radical neck dissection.[59,60] Such treatment decreases the incidence of local recurrence in the cervical nodes, especially when less than total thyroidectomy and no radioactive iodine is used, and this perhaps may improve survival.[60] Perhaps we should examine the nodal status of patients with papillary thyroid cancer with ultrasonography to select those patients with large nodes, as they are more likely to have involved nodes. A modified neck dissection that preserves the sternocleidomastoid muscle, spinal accessory nerve, and internal jugular vein might be indicated for these patients.

Previous studies documented that when patients were matched by age and sex, those with differentiated thyroid cancer of follicular cell origin who had clinically palpable cervical lymph nodes had a higher recurrence and death rate at all ages of life.[27] The EORTC study also documented that having palpable cervical metastases had an adverse effect on survival, although the presence of palpable cervical nodes is a minor rather than a major risk factor.[19,27] In another study using univariate and multivariate analyses, it was reported that lymph node metastases adversely influence recurrence and sur-

Patients with matted or clinically fixed nodes also appear to have a worse prognosis.[62] These patients should be treated by a modified radical or en bloc neck dissection that preserves the sternocleidomastoid muscle, spinal accessory nerve, and in most cases, the internal jugular vein. We do this dissection using the MacFee lateral extension of the Kocher transverse collar incision.[63] Most patients can be discharged within 48 hours of this procedure without adverse functional or cosmetic sequelae.

In summary, the presence of cervical lymph node metastases in patients with thyroid cancer indicates more extensive disease. These patients have an increased recurrence rate and seem to have a slightly worse prognosis.[19,27] The overall prognosis remains good, however.[4,19,27,28] Therapeutic modified radical neck dissection is generally recommended.

Extent of Therapy

The value of more extensive surgical treatment such as total thyroidectomy and the use of radioactive iodine is also debated for patients with papillary thyroid cancer. Numerous studies have shown that about 80% of patients with papillary thyroid cancer have micrometastases in their cervical lymph nodes at the time of thyroidectomy, and about 10% to 15% have occult pulmonary metastases despite no clinical evidence of tumor.[23,55,56] Despite this observation, clinically recurrent disease develops in the cervical nodes of only about 8% to 20% of patients. Many microscopic tumors must therefore remain occult or are ablated by the administration of radioactive iodine.

Numerous studies support the use of postoperative radioactive iodine, but no prospective studies have been done. In one study of 576 patients with papillary thyroid cancer, it was found that for lesions greater than 1.5 cm, the recurrence rate was 13.1% when patients were not treated with postoperative radioactive iodine and 6.4% when they received sodium iodide I 131($P < .001$ by Cox regression analysis).[5] In another study, patients with follicular thyroid cancer who were treated with radioactive iodine had a five-year survival rate of 100%, whereas the survival rate was 33.3% in untreated patients.[64] Patients with papillary thyroid cancers larger than 1 cm had fewer recurrences ($P < .01$) and fewer deaths when treated with radioactive iodine ($P < .05$; χ^2 analysis).[6] Fewer patients were reported to have pulmonary metastases develop, and fewer died when they were treated by total thyroidectomy and ^{131}I-sodium iodide therapy.[65] Other investigators noted that two thirds to three fourths of patients whose pulmonary metastases were detected only by radioiodine scanning were likely to be successfully treated, whereas when macrometastases were identified on chest x-ray film or computed tomographic scan, only 4% to 10% of patients could be cured.[35,66] Thus, when macronodular disease was present, the relative risk of death increased sixfold. Further data supporting the prophylactic use of ^{131}I-sodium iodide for patients with differentiated thyroid cancer is provided by Wong and associates.[67] Their use of radioactive iodine reduced the recurrence rate of thyroid cancer by 54%. The change in life expectancy gained by the ablation of thyroid remnants was about equal to that gained by lowering serum cholesterol levels to less than 5.20 mmol per liter (<200 mg per dl) in 35-year-old adults or by coronary artery bypass in patients with two-vessel coronary artery disease.

Despite the fact that the value of treating patients with radioactive iodine has been questioned[68] and that some think that radioactive iodine therapy is only as effective as thyroid hormone suppression therapy,[69] the vast majority of data suggest that prophylactic treatment with radioactive iodine is therapeutically efficacious.[2,4–6,25,35,66]

Radioactive iodine therapy, unfortunately, is less effective when metastatic thyroid cancer is clinically evident.[35,66,70] For example, the use of radioactive iodine was effective for treating patients with nonpalpable cervical lymph node metastases,[5] but it was rarely, if ever, effective in ablating clinically palpable nodes.[71] In contrast, when relatively large doses of ^{131}I-sodium iodide are used, a 74% success rate in treating nodal disease is reported.[72] Maxon says that when the projected radiation dose to the tumor is less than 30 Gy (3,000 rad), he prefers surgical excision, but he does not say how often this occurs.[25] The response of pulmonary micrometastases and macrometastases to ^{131}I-sodium iodide has already been discussed briefly.[35,66,70] In an analysis of the five-year mortality in patients with pulmonary metastases, the mortality was 38% in patients whose metastases concentrated radioactive iodine and 69% in those whose metastases did not ($P < .001$).[36]

Patients with skeletal metastases have an even poorer response to treatment with radioactive iodine, and the presence of bony metastases predicts an ominous prognosis. Unfortunately, about 70% of bony metastases are multiple and 30% solitary, and only about 10% of these usually lytic bone metastases take up radioactive iodine. A similar number of patients respond to treatment after ^{131}I-sodium iodide therapy (about 8%), so that external radiation therapy is often required.[25] The data concerning clinically evident metastatic thyroid cancer suggest that when cervical lymph nodes or pulmonary or skeletal metastases can be completely removed surgically, this should be done. The patient should then receive a large ablative dose of radioactive iodine (about 150 mCi). Serum thyroglobulin levels, especially when patients are hypothyroid in preparation for a radioiodine scan, are useful in determining the presence of persistent disease.

Conclusion

Most patients with differentiated thyroid cancer have an excellent prognosis. Numerous clinical and laboratory techniques are available that help predict whether a particular tumor will behave in an aggressive or benign manner. Until better predictors of tumor behavior are available, such as the presence or absence of certain oncogenes or tumor suppressor genes, I advocate doing total

thyroidectomy with the removal of central neck nodes and a modified radical neck dissection when the lateral neck nodes are clinically involved. I and others recommend that radioactive iodine be used postoperatively for all but low-risk patients and for patients whose tumors take up radioactive iodine.[73] I also recommend treatment with ^{131}I-sodium iodide for patients with elevated thyroglobulin levels whose metastatic thyroid cancers are not evident on routine scanning after total thyroidectomy.[74-77] We will prescribe enough thyroid hormone to suppress TSH production. Such combined therapy seems to result in fewer recurrences and better survival than less aggressive initial therapy.

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Epitomes

Important Advances in Occupational Medicine

Occupational Medicine

Ann Dew, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in occupational medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Occupational Medicine of the California Medical Association, and the summaries were prepared under the direction of Ann Dew, MD, and the panel.

Preventing Workers' Hepatitis A, B, C, D, E, and G

OCCUPATIONAL HEPATITIS is debilitating, deadly at times, but now preventable. When last studied, there was 1.4- to 2-fold excess mortality from cirrhosis in each of the three California female health care occupations measured—registered nurses, licensed vocational nurses and aides, and other—in whites or blacks after adjustment for age, alcohol use, and smoking. The recent documentation of numerous patients infected with hepatitis B by a California cardiovascular surgeon and the finding of hepatitis C (and possibly A and E) in patients of caregivers infected with those viruses further points out the high risks from health care workers with hepatitis infections.

The primary prevention of hepatitis relies both on reducing exposure (sanitation and avoidance of blood and body fluids) and vaccination for hepatitides A and B. Sanitary measures help prevent the primarily fecal-oral transmission of hepatitis A and E. Travelers to areas endemic for these viruses should avoid food or drink that is not commercially packed, purified, peeled in a sterile manner, or piping hot (the 4 *p*'s). Hepatitis A outbreaks have occurred in workers in day-care centers and in hospital pediatric units with eating, drinking, and insufficient hand washing at the work site.

Health care workers are at risk for chronic hepatitis B, C, D, and G through occupational exposure to blood or body fluids. Double gloving (with powder-free latex) and improved instruments and techniques are increasingly available to reduce such exposure.

Hepatitis G RNA was present in 13% of cases of acute hepatitis non-A to E from sentinel counties and 13 (1.7%) of 779 consecutive blood donors with normal alanine aminotransferase levels. Preventing blood exposure should help prevent the possible occurrence of occupational hepatitis G and its similarly transmitted relative, hepatitis C.

Vaccines can protect virtually any worker from hepatitides A, B, and D. Hepatitis A vaccination is recommended for workers in child day care, caretakers of developmentally disabled persons, those who do hepatitis A virus laboratory work, and those who travel to endemic areas. Recombinant hepatitis B vaccine induces protective antibody levels in a fourth or more of workers per dose, whether in the primary three-dose deltoid intramuscular series or as an intramuscular fourth, fifth, or intradermal 5-μg sixth through ninth dose for previous nonresponders. Primary responders show protection from occupational risks for five or more years and from nonoccupational risks for nine or more years. All seven responders to the intramuscular fourth dose showed an anamnestic-type response (suggesting protection) when given a booster dose at six years, despite a prebooster loss of antibody in five persons.

Secondary prevention (presymptomatic treatment) of occupational hepatitis C relies on interferon treatment's high efficacy in acute hepatitis C, as suggested by studies abroad. Percutaneous inoculation from hepatitis C virus (HCV)–positive patients infects 1% of the workers receiving exposure. Hepatitis C virus exposure may occur from the HCV–positive 1% (hospital-based surgeon volunteers from 2 cities) to 18% (urban emergency department patients) to 93% (northern California drug treatment clinics' intravenous heroin users) of populations in the United States.

BRUCE N. LEISTIKOW, MD, MS
Davis, California

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Long-Term Effects of Air Pollution

LONG-TERM HEALTH EFFECTS from smog can be insidious. This is unlike some of the obvious, immediate health effects from smog, such as the development of burning eyes and headaches in people visiting the Los Angeles, California, area when air pollution levels are at their worst. Long-term effects from smog are also not nearly as pronounced as those found from cigarette smoking, for instance. Many people in the United States and other countries have substantial exposure to air pollutants, however, and even a small effect can translate into a serious health problem. This is of particular concern in California, which has some of the worst air pollutant levels in the nation. The Riverside–San Bernardino area consistently has some of the highest levels in the nation for both particulates and ozone, considerably above the national ambient air quality standard.

A cohort of more than 6,000 adult nonsmoking Seventh-Day Adventists in California has been observed since 1977. Pollutant concentrations for persons were estimated from the California Air Resources Board monitoring stations. Pollutants studied included total suspended particulates, suspended sulfates, and gaseous pollutants such as ozone.

The development of respiratory disease was shown to be related to exposure to total suspended particulates. Persons who had lived for 20 years in areas with elevated levels of total suspended particulate had an increased risk of 36% for the development of airway obstructive disease, which includes asthma, chronic bronchitis, and emphysema. The development of chronic bronchitis had a 33% elevated risk for those with exposure to higher levels of total suspended particulates. Exposure to lower concentrations of these particulates was also associated with an elevated risk of airway obstructive disease, particularly when the exposure was for an extended time period. In areas with substantial air pollution, such lower levels can commonly occur for extended periods and thus contribute substantially to the overall health effects from smog.

In considering the development of respiratory diseases, tobacco smoke exposure is extremely important. Tobacco smoking is strongly associated with the development of airway obstructive disease. Also, environmental tobacco smoke exposure, from either home or work, shows an association with the development of airway obstructive disease. Each of these must be considered when evaluating the clinical effects of air pollution. Childhood symptoms of airway obstructive disease and childhood colds are both significant predictors for the development of the disease.

The development of asthma in nonsmokers had a pronounced association with airway obstructive disease present before age 16, with a more than fourfold increase in risk. Recent findings also indicate an influence from a parental history of airway obstructive disease. These findings indicate that some persons have increased susceptibility to the development of asthma. A more than threefold increased risk of asthma was found in men who had lived 20 years in areas with high ozone levels. For women, however, the risk was not significantly elevated. The lack of an effect in women is postulated to be due to their spending less time outdoors and thus having less occupational exposure to air pollutants in general and, in this case, specifically to ozone. The development of asthma also showed a more than twofold elevation in risk associated with exposure to suspended sulfates. Secondhand smoke exposure also was significantly associated with the development of asthma, with a 45% increased risk.

Exposure to total suspended particulates is further associated with an elevated risk of 37% for the development of all malignant neoplasms in women. Exposure to fine particulates was specifically associated with a twofold elevation in risk for all malignant neoplasms in women. This effect is not seen in men. Women have been shown to have a greater deposition fraction than men of fine particles in the lungs. These fine particulates often contain the most toxic compounds, and this may explain the difference between men and women in the effect of particulates.

In a study of six US cities, significant associations were found between air pollution mortality, with an elevated risk of dying of 26% in those living in areas of highest pollution. The air pollution was specifically associated with deaths from lung cancer and from cardiopulmonary disease.

DAVID BERGLUND, MD
DAVID ABBEY, PhD
Loma Linda, California

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Use of Nucleic Acid in the Diagnosis and Management of Tuberculosis Amplification Tests

TUBERCULOSIS is an ancient infection that has plagued humans throughout recorded history. A third of the world's population is infected with *Mycobacterium tuberculosis*, and it remains the most common infectious cause of morbidity and mortality worldwide, with an annual mortality approaching 3 million. In April 1993, the World Health Organization declared tuberculosis a global emergency. The diagnosis of this important disease has traditionally relied on conventional microscopy and culture, a process that can take as long as eight weeks. Nucleic acid amplification testing (NAAT), a new and exciting technology

for the rapid diagnosis of tuberculosis, has recently been developed that potentially allows a diagnosis of tuberculosis to be made within hours. The application of this new technology is expected to greatly assist physicians and public health programs in the diagnosis, management, and contact investigations of persons with tuberculosis.

Nucleic acid amplification testing is a rapid technique of amplifying either RNA or DNA that allows the creation of millions of identical copies of a specific genetic sequence that then serve as markers for the presence of organisms in biologic specimens. Although polymerase chain reaction is the most well-known NAAT, many others have been developed. Gen-Probe's *M tuberculosis* direct test (MDT), one version of NAAT, was recently the first to be approved by the Food and Drug Administration for the detection of *M tuberculosis* in sputum specimens that are smear-positive for acid-fast bacilli (AFB). It is expected that other manufacturers' tests will be approved within the next two years. The MDT is commercially available and requires only six hours to perform, allowing a rapid turnaround time of testing results. The performance of the Gen-Probe MDT has been well documented and has yielded excellent results compared with traditional smear and culture techniques used in diagnosing tuberculosis. The average sensitivity and specificity of the test for all published trials are 87% and 99%, respectively, resulting in a positive predictive value of 95% and a negative predictive value of 98%. This compares with the 54% sensitivity for fluorochrome stain, the rapid diagnostic test currently used to detect AFB. In our clinic, the fluorochrome stain misses the 46% of patients with tuberculosis with negative smears who are ultimately positive on culture, whereas NAAT misses only 18% of patients with cultures positive for tuberculosis. The sensitivity of NAAT for AFB smear–positive specimens (99%) is higher than that for AFB smear–negative specimens (56%).

Now that a NAAT for *M tuberculosis* is readily available, questions have been raised as to how to apply it most effectively in a clinical setting. It seems clear that with a specificity and positive predictive value approaching 100%, it is a reliable tool for the diagnosis of tuberculosis in a patient with a positive AFB smear. Although it is only 56% sensitive in AFB smear–negative specimens, a positive NAAT in a patient with a negative smear provides an early clue to the presence of active tuberculosis. The diagnosis of tuberculosis in these AFB smear–negative patients might otherwise be delayed, especially if they have minimal clinical or radiographic findings. Starting treatment immediately for these smear-negative patients avoids the potential of communicability developing during the interval of as long as eight weeks while awaiting culture results.

Nucleic acid amplification testing has limitations. About 18% of patients with culture-positive tuberculosis will be missed with this test. There are two explanations: few organisms in the submitted specimen and specimens that contain inhibitors. Controls can be used to rule out the presence of inhibitors for smear-positive NAAT-negative specimens. It is important not to withhold treatment in a patient who has clinical features consistent with active tuberculosis just because the NAAT is negative. It is always prudent to await final culture results and to assess the patient's response to treatment. It is appropriate to initiate the treatment of active tuberculosis in a smear-negative patient with a positive NAAT even if there is minimal clinical and radiographic evidence for the disease. Studies have shown that more than 90% of these patients will ultimately grow *M tuberculosis* in culture. Those patients who do not produce a positive culture may still have active tuberculosis but with an insufficient number of viable organisms to produce a positive culture in the laboratory. In these cases, a diagnosis of tuberculosis might otherwise be missed without adjunctive NAAT testing.

In summary, NAAT is becoming an important tool to aid in the diagnosis of tuberculosis, but it does not replace clinical evaluation, conventional AFB smears, and culture techniques. It has the ability to diagnose tuberculosis rapidly in 99% of AFB smear–positive specimens and in 65% of AFB smear–negative specimens. It is appropriate to initiate treatment based on the results of this test but not to stop treatment if results are negative until culture results become final. The use of NAAT has proved helpful to decision making in our public health practice. The test can be used as an early diagnostic tool to determine if an infection is caused by *M tuberculosis*. If the smear is positive, NAAT is particularly helpful in guiding decisions about contact investigations and the need for respiratory isolation in patients who may be infected with a *Mycobacterium* species other than tuberculosis. If the smear is negative, NAAT allows earlier treatment of tuberculosis other than waiting for culture. It has proved to be an effective tool in the diagnosis and management of tuberculosis. We think it will also prove to be effective in responding to the global epidemic of tuberculosis.

JODY MEADOR, MD
DOUGLAS MOORE, PhD
PENNY WEISMULLER, DrPH
Santa Ana, California

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Latex Allergy

THE PROBLEM OF cutaneous and respiratory reactions to latex antigen(s) is one that has generated considerable attention among allergists, anesthesiologists, surgeons, occupational medicine practitioners, and health care professionals in general. Whether the widely held perception that the prevalence of glove-related health prob-

lems is increasing among health care workers is due to heightened practitioner awareness or is a real phenomenon cannot be addressed directly with existing surveillance data. Nevertheless, the increasingly routine use of latex gloves as part of universal precautions, as well as the use of mass-produced examination gloves with relatively high antigen content, are factors pointing to an increased exposure potential—that is, more health care workers (and others) are wearing latex gloves and are doing so for a greater portion of their workweek.

Allergists and dermatologists first described immediate-onset latex-associated skin reactions in 1980, labeling them as immunoglobulin E–mediated contact urticaria. Subsequently, numerous cases of angioedema, anaphylaxis, rhinoconjunctivitis, and bronchospasm have been ascribed to latex allergy. The Food and Drug Administration did much to increase awareness of this issue when, in 1991, it issued a bulletin describing anaphylactic reactions to rubber-tipped barium enema catheters. This information encouraged anesthesiologists to investigate hitherto-unexplained intraoperative hypotensive events and to conclude that, in some cases, anaphylactic reactions to surgeons' gloves may be responsible. Issues of nonmedical latex exposure (for example, to condoms, chewing gum, and balloons) and of cross-reactivity with some foods (bananas, avocados, kiwi fruit, chestnuts, and others) have also been identified. Considerable effort has subsequently been invested in identifying the responsible antigenic determinants from the sap of the rubber tree, *Hevea brasiliensis*, and in perfecting skin test antigens and in vitro test reagents.

In the workplace—particularly in hospitals—latex allergy can be a vexing problem. First, latex-related skin conditions must be distinguished from more commonly occurring conditions, such as nonspecific glove-related exacerbation of dyshidrotic eczema and atopic dermatitis, and from less common disorders, such as allergic contact dermatitis from rubber accelerators or antioxidants. In making this distinction, the timing and morphology of skin reactions may be helpful, and in vitro diagnostic tests can help confirm latex allergy as part of a diagnostic algorithm. Nevertheless, specialty consultation for skin-prick or patch testing may be needed. For persons with respiratory symptoms, a similar approach is used, with the addition of peak flow measurements to document cross-workshift decrements in pulmonary function.

Once a latex allergy is diagnosed, the affected person must be supplied with appropriate gloves. For a person with atopic dermatitis or dyshidrotic eczema, the use of cloth glove liners is far more important than substituting glove materials. For a person with true latex skin allergy, substitute gloves are available fabricated from a variety of materials, including vinyl (polyvinyl chloride), nitrile (polynitrile), polychloroprene, and substituted polystyrene polymers. The most challenging situation is posed by persons with substantial respiratory symptoms. Cornstarch or talc dust on powdered latex gloves acts as an airborne antigen carrier and can therefore passively trigger respiratory symptoms in persons not wearing such gloves. Thus, in a hospital or clinic environment, it would be desirable to replace all powdered latex gloves with unpowdered, in addition to providing sensitized persons with nonlatex substitutes.

The major barrier to such a strategy at this time is economic. Although no substantial cost differential exists for replacing powdered latex "examination" (nonsterile) gloves with their unpowdered counterparts, a large differential (5 to 6 times the cost) exists for "surgeons'" (sterile) gloves. To dictate that all personnel in a given facility wear either unpowdered latex or nonlatex gloves, whether the persons are latex sensitized or not, may be an expensive step. On the other hand, excluding health care professionals from their customary employment may be an even costlier proposition. Under the Americans with Disabilities Act of 1990, a "qualified individual with a disability" has a right to "reasonable accommodation" with respect to working conditions, while "essential functions" of the job cannot pose an "imminent risk of harm." Accordingly, prudent occupational health practitioners carefully document any decision-making processes that affect the initial or continuing employment status of latex-sensitized workers. In such a climate, it is only a matter of time before market forces eliminate the cost differential between powdered latex surgeons' gloves and their unpowdered (or nonlatex) counterparts.

DENNIS SHUSTERMAN, MD, MPH
San Francisco, California

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Decreasing Work Disability From Asthma

ASTHMA PREVALENCE is increasing, and many cases have occupational and environmental causes. Unlike many other respiratory problems, it affects people during their active working life and can substantially affect their ability to work. The overall cost to patients and employers is great. Public health and clinical approaches can decrease its burden. A notable proportion of asthma is caused by work; this is known as "occupational asthma." It is more frequently of nonoccupational origin, but is aggravated by occupational exposure; this is known as "work-aggravated asthma."

There are two major categories of occupational asthma: "with latency" (delay between exposure and onset) and "without latency." Occupational asthma with latency often depends on the development of antibodies and therefore requires time and repeated exposures to a specific antigenic

agent. Occupational asthma without latency is not allergic in nature. Nonoccupational asthma aggravated by work is due to nonspecific irritant responses. In addition, workers with nonoccupational asthma may have work disability because of an inability to meet a job's physical demands.

Several methods can prevent or limit work disability from occupational asthma with latency: Primary prevention of occupational asthma generally depends on limiting exposures known to cause the asthma. Secondary prevention of occupational asthma depends on early recognition and removing the patient completely from further exposure. In addition, recognizing the disease in one person may allow the complete prevention of it in others by controlling exposures.

Reactions to specific workplace chemical agents (such as latex or diisocyanates) may develop in sensitized persons with exposure to extremely low levels (parts per billion). Secondary prevention—early recognition of the disease—is particularly important for occupational asthma. Several studies have shown that once occupational asthma with latency begins, a delay in removing the worker from further exposure worsens the prognosis for recovery. Personal socioeconomic factors may interfere with a patient's following the physician's advice about avoiding exposure. The early initiation of vocational retraining can substantially decrease the length and extent of occupational disability. These disorders have major economic effects for patients and employers; early identification by primary practitioners and careful confirmation by physicians with particular skill in occupational and pulmonary medicine can limit both delays and overdiagnosis.

Other approaches are best for limiting disability from occupational asthma without latency and work aggravation of nonoccupational asthma. Good patient education and pharmacologic control of asthma severity are important, but many factors other than disease severity affect work ability and motivation. Asthma without latency is clinically similar to nonoccupational asthma and does not imply sensitization to a specific workplace chemical agent. Persons with occupational asthma without latency may often be accommodated in the workplace by measures such as improved ventilation, good workplace housekeeping practices, and the use of respirators. In addition, modification of the job to decrease peak ventilatory demand is often feasible and may be supported by the Americans with Disabilities Act.

PHILIP HARBER, MD
Los Angeles, California

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University of California Occupational Health Programs Statewide Advisory Comittee
Alameda

Alerts, Notices, and Case Reports

Propylthiouracil-Induced Hepatotoxicity

JAMES T. HARDEE, MD
ANGELA L. BARNETT, MD
ABDUL THANNOUN, MD
BIJAN EGHTESAD, MD
DONALD WHEELER, MD
M. MAZEN JAMAL, MD
Albuquerque, New Mexico

PROPYLTHIOURACIL (PTU) is a thioamide derivative widely used in the treatment of hyperthyroid conditions. Despite its relatively safe profile, hepatotoxicity remains a serious, albeit rare, complication. Having been reported in nearly 30 cases in the English-language literature since its introduction in 1947,[1–26] PTU-induced toxic liver injury must be considered in any patient receiving this drug in whom symptoms of hepatic dysfunction appear. Patients may present with jaundice, right upper quadrant abdominal pain, malaise, nausea, vomiting, and anorexia. Reported sequelae of PTU hepatotoxicity range from rapid recovery following discontinuation of the drug* to fulminant hepatic failure and death.[2,3,12,13,18] A recent review of drug hepatotoxicity lists PTU-induced hepatitis as an "idiosyncratic" reaction with immunologic mechanisms, hypersensitivity, and direct toxicity among the postulated pathogeneses.[27]

A patient was recently transferred to our institution whose condition fit the description of PTU-induced hepatic failure. We report the case and describe the histopathologic findings on liver biopsy.

Report of a Case

The patient, a 37-year-old woman, was diagnosed with Graves' disease five months before her presentation, and a regimen of oral propylthiouracil, 200 mg per day, was started. At that time, baseline laboratory values were as follows: alkaline phosphatase, 298 IU per liter (normal, 130 to 150); total bilirubin, 17.1 μmol per liter (1.0 mg per dl [normal, 2 to 18 μmol per liter]); direct bilirubin, 3.4 μmol per liter (0.2 mg per dl [normal, 0 to 4 μmol per liter]); and aspartate aminotransferase (AST), 20 IU per liter (normal, 14 to 34). Two months later, the dose of PTU was increased to 400 mg daily for persistently elevated serum thyroid hormone levels. The patient tolerated this dosage for nearly three months until she contacted her primary physician because of weakness, fever, chills, nausea, vomiting, and a sharp right upper quadrant abdominal pain for several days. Also, her children had remarked about her "yellowish" appearance.

Propylthiouracil was discontinued at that time, and she was observed on an outpatient basis. Three days later, she was admitted to a community hospital for worsening malaise, jaundice, and nausea. Laboratory values on admission were as follows: thyroxine, 178 nmol per liter (13.8 μg per dl [normal, 51 to 142 nmol per liter]); AST, 1,490 IU per liter; alanine aminotransferase (ALT), 1,135 IU per liter (normal, 9 to 52); alkaline phosphatase, 486 IU per liter; total bilirubin, 284 μmol per liter (16.6 mg per dl); direct bilirubin, 169 μmol per liter (9.9 mg per dl); and prothrombin time, 15.5 seconds (control, 9.4 to 13.3 seconds). Tests for hepatitis A antibody immunoglobulin (Ig) M, hepatitis B surface antigen, and hepatitis B core antibody were all negative. A right upper quadrant abdominal ultrasonogram showed no sign of biliary dilation, and the liver, pancreas, and kidneys all appeared normal. By the second hospital day, her prothrombin time had increased to 17.2 seconds, and she was showing no signs of clinical improvement; she was thus transferred to our institution for evaluation.

On arrival at the University of New Mexico Health Sciences Center, Albuquerque, the patient was alert, deeply jaundiced, and continuing to have sharp, achy, right-sided abdominal pain. On questioning, she reported no recent travel history and no acetaminophen, alcohol, or injection drug use. She had no history of hepatitis exposure, blood transfusion, or other ingestions.

Her medical history was notable only for two vaginal deliveries, a postpartum tubal ligation, and a six-month history of hyperthyroidism. The patient was taking no medications as PTU had been discontinued five days before her transfer.

On physical examination, the patient was afebrile with a blood pressure of 134/73 mm of mercury, a pulse rate of 95 beats per minute, and a respiratory rate of 16 per minute. Chest auscultation revealed clear breath sounds bilaterally and a regular cardiac rate and rhythm without murmur. Her skin was jaundiced, and her sclerae were icteric; exophthalmos and lid lag were apparent. There were no stigmata of chronic liver disease. Her neck was supple, and the thyroid gland was three times normal size, smooth, firm, and nontender, with a prominent isthmus. Her abdomen was soft with moderate tenderness to palpation in the right upper quadrant. No guarding or rebound tenderness was noted, and no hepatosplenomegaly was appreciable. There was no asterixis or tremor, and deep tendon reflexes were normal.

Tests for hepatitis A antibody IgM, hepatitis B surface antigen, and hepatitis B core antibody were repeated and confirmed to be negative, as was a test for hepatitis C RNA by polymerase chain reaction. An erythrocyte sedi-

*References 1, 4–11, 15, 16, 19, 22, 23, 25, and 26.

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From the Department of Internal Medicine, Division of Gastroenterology (Drs Hardee, Barnett, Thannoun, and Jamal); the Department of Surgery, Division of Liver Transplantation (Dr Eghtesad); and the Department of Pathology (Dr Wheeler), University of New Mexico School of Medicine, Albuquerque.

Reprint requests to James T. Hardee, MD, Department of Internal Medicine, University of New Mexico Health Sciences Center, 2211 Lomas Blvd NE, Albuquerque, NM 87106.

ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
ANA = antinuclear antibody
AST = aspartate aminotransferase
CMV= cytomegalovirus
EBV = Epstein-Barr virus
Ig = immunoglobulin
PTU = propylthiouracil

mentation rate was normal at 7 mm per hour, an antinuclear antibody (ANA) titer was 1:320, and an anti–smooth muscle antibody titer was 1:40. Tests for antimitochondrial antibody, antimicrosomal antibody, anticentromere antibody, and antihistone antibody IgG were all negative. An Epstein-Barr virus (EBV) IgG test was positive at 1:640, indicating previous exposure to EBV, and a CMV IgG level was within normal limits at 81.3 Antibody Units per ml. Cultures of blood and urine were negative for growth.

The patient underwent a transjugular liver biopsy on hospital day 1, which subsequently revealed severe acute hepatitis with portal-to-central-bridging necrosis (Figure 1). A transjugular approach was chosen to minimize bleeding complications because her prothrombin time had climbed to 21.4 seconds. Her condition continued to deteriorate on hospital day 2, as shown by the following laboratory values: ALT, 1,449 IU per liter; AST, 2,052 IU per liter; alkaline phosphatase, 485 IU per liter; total bilirubin, 369 μmol per liter (21.6 mg per dl); direct bilirubin, 299 μmol per liter (17.5 mg per dl); and prothrombin time, 21.9 seconds. During this time, she had episodes of hypoglycemia, tachycardia, and mental status changes and was transferred to the medical intensive care unit for closer monitoring. Radioactive iodine ablation of the thyroid was not attempted because of the iodine-containing contrast medium given the patient during fluoroscopic transjugular biopsy. A regimen of intravenous methylprednisolone sodium succinate (80-mg load, followed by 60 mg every 8 hours), lithium carbonate, and propranolol hydrochloride was started for the control of thyrotoxicosis. Within 48 hours, an improvement was noted in the following laboratory values: ALT, 894 IU per liter; alkaline phosphatase, 369 IU per liter; total bilirubin, 315 μmol per liter (18.4 mg per dl); direct bilirubin, 299 μmol per liter (14.5 mg per dl); and prothrombin time, 28.4 seconds. She was then transferred out of the intensive care unit on a tapering course of oral prednisone with continued clinical and laboratory improvement. By hospital day 6, laboratory values were as follows: ALT, 456 IU per liter; AST, 187 IU per liter; alkaline phosphatase, 290 IU per liter; total bilirubin, 255 μmol per liter (14.9 mg per dl); direct bilirubin, 197 μmol per liter (11.5 mg per dl); and prothrombin time, 19.6 seconds.

The patient was discharged to home on hospital day 11 on a regimen of lithium carbonate and a tapering course of oral methylprednisolone and was scheduled for definitive thyroid treatment.

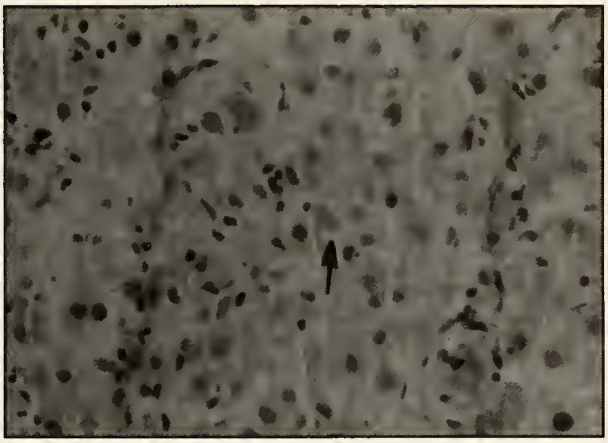

Figure 1.—A transjugular liver biopsy is shown (original magnification × 400). Prominent mononuclear cell infiltrate is present throughout the lobules. Numerous acidophil bodies are identified **(arrow)**.

Discussion

Although propylthiouracil has been used safely for many years in the treatment of hyperthyroid conditions, several adverse reactions have been reported, including agranulocytosis,[28] leukopenia,[29,30] hemolytic anemia,[31] aplastic anemia,[32] disseminated intravascular coagulation,[33] cutaneous vasculitis,[34,35] and interstitial pneumonitis.[36]

Hepatotoxicity from PTU has been one of the most widely described adverse reactions. A cohort study in 1993 revealed that ALT values became elevated in 33% (15 of 45) of patients studied after two months of PTU administration.[24] These elevations were transient, abating with the reduction in medication dose over time, and the patients were asymptomatic. The temporal relationship between ALT elevation and the start of PTU treatment suggests that the elevation was indeed induced by PTU use, thus reflecting subclinical acute hepatocellular injury evidenced by aminotransferase leakage. The conclusion was that these findings contradict previous observations that PTU-induced hepatitis is rare and usually severe.

Drug-induced hepatocellular injury is a difficult diagnosis to establish and is often one of exclusion. Etiologic agents that must be investigated include hereditary disorders, viral infections (including hepatitis A, B, C, CMV, and EBV), and other hepatotoxins. It has also generally been accepted that hyperthyroidism itself can cause abnormalities in liver function test values. In one series, liver biopsy specimens of patients with thyrotoxicosis were examined, and Graves' disease was found to be associated with minimal hepatic changes and mild elevations of liver enzyme levels.[37] Ideal and practical criteria were proposed in 1984 to assist in the diagnosis of drug-induced hepatitis. Ideal criteria would include the histologic confirmation of hepatocellular injury and drug rechallenge, but this is seldom ethically possible. Practical criteria should include clinical and laboratory evidence of hepatocellular dysfunction; the onset of symptoms temporally related to the start of drug therapy;

no serologic evidence for current infection with hepatitis A, B, or C, CMV, or EBV; the absence of an acute hepatic insult such as shock or sepsis; no evidence of chronic liver disease; and the absence of other concomitantly administered drugs, especially known hepatotoxins.[13]

In the past, it has been difficult to ascribe characteristic histologic features to PTU-induced hepatitis due to the small number of biopsies actually done. Of the ten documented cases of PTU-induced hepatitis in which liver biopsies were taken, histopathologic features have ranged from mild portal inflammation to submassive or massive hepatic necrosis with bridging fibrosis.[2-6,10,12,18,19,26]

In 1976 the case of a 24-year-old woman with PTU hepatitis who underwent liver biopsy three weeks after her initial presentation was described. The biopsy showed hepatocellular necrosis with lobular disarray, free acidophil bodies, ballooning degeneration, and bridging necrosis.[6] A postmortem examination of liver disease performed on a 20-year-old woman with PTU hepatitis in 1982 revealed hepatic nodules and fatty degeneration consistent with fibrosis following submassive hepatic necrosis.[12] A 56-year-old man with PTU hepatitis had acute and chronic inflammatory cells on percutaneous liver biopsy performed two days after his presentation. Under electron microscopy, the specimen revealed autophagic vacuoles, residual bodies, both contracted and swollen mitochondria, and dilated, smooth endoplasmic reticulum.[5]

Microscopic examination of the transjugular liver biopsy specimen in our patient revealed a prominent mononuclear infiltrate throughout the lobules, and numerous acidophil bodies were identified in a background of pronounced hepatocellular dropout (see Figure 1). There was occasional interstitial hemorrhage in the central regions, and the portal tracts contained a pronounced mononuclear cell infiltrate, predominantly lymphocytes. An iron stain was negative, and there was no evidence of hyaline globules, viral inclusions, granulomas, or neoplasia. The histologic features were consistent with severe acute hepatitis with portal-to-central-bridging necrosis.

Although a regimen of intravenous steroids was initiated to control the patient's thyrotoxic state, a rapid improvement in aminotransferase and bilirubin levels and prothrombin time was incidentally noted. Whether this improvement was due in part to the steroid therapy or simply to the discontinuation of PTU seven days earlier is unclear. A search of the literature found no record of controlled or uncontrolled trials of corticosteroid treatment of drug-induced hepatitis, and the efficacy of this therapy can only be described as anecdotal at this time.

This case has been attributed to PTU toxicity because it fulfills Hanson's criteria.[13] Before treatment with PTU, our patient had no clinical or biochemical evidence of hepatic dysfunction. The marked rise in aminotransferase levels and the close temporal relationship of these changes to the start of PTU therapy again supports this diagnosis. It should be noted that given the positive ANA test (1:320) and the slightly positive anti–smooth muscle antibody test (1:40), the possibility of autoimmune hepatitis cannot be completely ruled out. Antinuclear antibody titers can be elevated in many conditions involving hepatocellular damage, and the obvious temporal relationship to PTU therapy makes this the most likely cause.[38]

Because an early recognition of PTU-induced hepatic failure and prompt withdrawal of the drug may prevent progression from mild to severe disease, it may be prudent to discuss signs and symptoms of liver disease and other side effects with patients. Jaundice, pruritus, dark urine, abdominal pain, anorexia, or malaise should signal a patient to seek medical attention.

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Venlafaxine Hydrochloride and Chronic Pain

KIRK TAYLOR, MD
MICHAEL C. ROWBOTHAM, MD
San Francisco, California

CLINICAL TRIALS of tricyclic antidepressants have shown efficacy for both chronic headaches and neuropathic pain.[1] The tricyclic antidepressants useful for chronic pain block the neuronal reuptake of both serotonin and norepinephrine. Serotonin-selective reuptake-inhibitor antidepressants have shown little or no efficacy when compared with placebo or tricyclic antidepressant use for neuropathic pain.[2] Unfortunately, the use of these drugs for chronic pain is limited by numerous side effects such as sedation, cognitive impairment, orthostatic hypotension, cardiac conduction abnormalities, dry mouth, and constipation. Many of these effects are due to the affinity of tricyclic antidepressants for the muscarinic-cholinergic, histaminic, and α_1-adrenergic receptors. Venlafaxine hydrochloride is a new antidepressant medication that, like the tricyclic antidepressants, inhibits the neuronal reuptake of both serotonin and norepinephrine.[3] Venlafaxine does not bind to muscarinic-cholinergic, histaminic, and α_1-adrenergic receptor sites, making its side effect profile substantially different from and theoretically more benign than that of the tricyclic antidepressants.

We report our initial open-label experience with venlafaxine in treating patients with chronic pain, primarily headache and neuropathic pain. Pain relief was rated by combining a patient's rating of efficacy with the clinician's global impression after a minimum of four weeks of therapy. If a patient completed less than four weeks of treatment, efficacy was rated at the end of treatment. An 80% or greater reduction in pain severity was interpreted as complete pain relief, a 50% to 79% reduction as moderate pain relief, 20% to 49% as mild pain relief, and less than 20% reduction in pain as no pain relief.

Summary of Cases

Table 1 summarizes the cases of the first 12 patients we treated with venlafaxine. All of them had had inadequate pain relief or intolerable side effects with the use of at least one antidepressant. These patients completed at least two weeks of therapy with venlafaxine. One case was not included in the results because the patient had severe nausea after taking only two doses. Otherwise, the data were collected over a seven-month period after patients were examined for chronic pain or headache.

The eight women and four men had an average age of 54 years and an average pain duration of 7.7 years. Four patients had headache, seven had neuropathic pain, and one had atypical facial pain. Patients had tried an average of 2.6 different antidepressants before taking venlafaxine. Patients 6 and 10 were on concurrent opioid therapy with transdermal fentanyl citrate patches. Patients 5 and 9 did not complete four weeks of therapy. Patient 5 had complete relief of chronic daily headache for two weeks, but when pain began to return, she elected to discontinue venlafaxine instead of adjusting the dose. Patient 9 was taking several medications—mexiletine hydrochloride, carbamazepine, and valproate sodium—for pain due to a posterior fossa arteriovenous malformation after a stroke. With the start of venlafaxine therapy, an increased blood pressure required the cessation of fludrocortisone acetate used for the control of orthostatic hypotension. The patient experienced persistent drowsiness and unsteady gait after three weeks of therapy, and venlafaxine was discontinued. In the other ten patients, pain relief was rated as moderate in seven and mild in three at total daily dosages from 18.75 to 250 mg per day (average, 99 mg per day). The most common side effect was nausea, which was made manageable by starting therapy at 18.75 mg per day. Patient 10 had moderate relief of peripheral neuropathic pain at a dose of 37.5 mg per day but later reduced the dose to 18.75 mg per day because of subjective hyperthermia and impotence, with only a slight diminution of pain relief. Patient 12 later required a dose reduction from 75 mg twice a day to 37.5 mg twice a day because of worsened hypertension. She became normotensive without a loss of pain control. Based on these results, ven-

(Taylor K, Rowbotham MC: Venlafaxine hydrochloride and chronic pain. West J Med 1996; 165:147–148)

From the Pain Management Center, the Departments of Neurology and Anesthesia, University of California, San Francisco (UCSF), School of Medicine

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Reprint requests to Michael C. Rowbotham, MD, UCSF Pain Management Center, 2233 Post St, Ste 104, San Francisco, CA 94115.

TABLE 1.—*Patients Treated With Venlafaxine Hydrochloride (HCl)*

Patient	*Age, yr*	*Sex*	*Diagnosis*	*Duration, yr*	*Antidepressant Drug Trials*	*Venlafaxine HCl Dosage, mg/d*	*Dose Response*
1	30	Female	Reflex dystrophy	1	Desipramine HCl	75, 2×	Mild relief
2	42	Female	Migraine	10	Nortriptyline HCl, amitriptyline HCl	37.5	Moderate relief
3	44	Male	Intercostal neuralgia	9	Amitriptyline, fluoxetine, nortriptyline	125, 2×	Moderate relief
4	45	Female	Atypical facial pain	11	Desipramine, imipramine HCl, doxepin HCl, nortriptyline	37.5	Moderate relief
5	47	Female	Mixed headache	18	Nortriptyline, amitriptyline, paroxetine	75, 4×	Complete relief
6	50	Female	Multiple sclerosis	5	Amitriptyline	37.5	Mild relief
7	52	Female	Mixed headache	15	Amitriptyline, fluoxetine, sertraline, paroxetine	75	Moderate relief
8	53	Male	Peripheral neuropathy	3	Amitriptyline, fluoxetine	50, 4×	Moderate relief
9	65	Male	Poststroke pain	5	Amitriptyline, desipramine	37.5	Moderate relief
10	70	Male	Peripheral neuropathy	6	Desipramine, amitriptyline, doxepin	37.5	Moderate relief
11	71	Female	Mixed headache	2	Nortriptyline, paroxetine	37.5	Mild relief
12	74	Female	Postzoster pain	7	Desipramine, amitriptyline, imipramine, sertraline	75, 2×	Moderate relief

lafaxine provided substantial relief in patients who were refractory to treatment with other antidepressants.

Conclusion

Venlafaxine appears to be a useful addition to the list of antidepressants with efficacy in pain management. Like other antidepressants, side effects are minimized by starting at the lowest possible dose. Increased blood pressure and nausea seen with venlafaxine are uncommon with the use of tricyclic antidepressants, and antidepressant-like cognitive impairment and anticholinergic side effects were uncommon with the use of venlafaxine. This open-label experience supports the need for controlled, randomized clinical trials of venlafaxine for chronic pain.

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Topics in Primary Care Medicine

Action Plans in Asthma Management
Why, When, and How?

SUSAN JANSON, DNSc, RN, *San Francisco, California*

The rising prevalence, morbidity, and mortality of asthma have focused national attention on the management of asthma, a chronic inflammatory disorder of the airways. There are about 5,000 deaths from asthma in the United States per year, but the most alarming facts are that the rate is rising and that most of these deaths appear to be preventable.[1-3] Asthma deaths have been attributed to the underrecognition of increasing asthma severity by both patients and their health care practitioners, undertreatment, lack of follow-up care, the failure to objectively measure pulmonary function, and the failure to provide a detailed treatment plan.[4] These observations have received national attention in the public and scientific press and have led to a national call for the development of public health interventions to address the problem of asthma morbidity and mortality in the United States.[3] Preventing death from asthma requires the recognition of those at risk and interventions to reduce risk, including appropriate pharmacotherapy and patient education.[5]

Undertreatment and the lack of a clear treatment plan are two factors that may influence the outcome of the disease.* In one study of asthma management in 111 persons with asthma presenting to an emergency department with acute symptoms, inadequate treatment and lack of a plan were clearly identified as major problems.[6] Nearly 30% of the patients were being treated with a β-agonist agent alone, with no anti-inflammatory therapy at all, and 37% of the sample had no idea what to do in the event of an acute attack (no action plan). Clearly, pharmacologic therapy must be appropriately prescribed in adequate doses, but equally important, patients with asthma require consistent follow-up and a clearly written treatment plan that includes more than a list of medications, doses, and dosing times. If patients are to know what to do when an acute flare of asthma develops, the written treatment plan must include specific directions about how to recognize worsening asthma and when to seek urgent care. To emphasize the behavioral response required, these plans have been called asthma action plans. Because symptoms are often unreliable indicators of airflow obstruction, published practice guidelines advocate the use of peak flow–based action plans in addition to signs and symptoms.[7-9]

Several studies have shown that action plans can be effective methods of asthma self-management that improve pulmonary function and reduce histamine responsiveness, the number of urgent care visits, work or school absences, and the need for a rescue course of oral prednisone.[10-14] Many agree that most patients with asthma can benefit from both verbal individualized advice about asthma and individualized, written self-management plans.[15-17]

What Is an Asthma Action Plan?

An action plan is a written set of instructions for patients and family to guide them in self-managing an asthma exacerbation. The plan can be based on peak flow measurements or key warning signs and symptoms, but may be most effective if it includes a combination of all three. The symptoms of asthma—dyspnea, chest tightness, and wheezing or coughing—worsen during asthma exacerbation but do not directly correlate with increasing airflow obstruction. Therefore, it is important to provide patients with objective indicators as well, such as critical peak flow values and observable signs, including waking at night wheezing, having activity intolerance, and having an escalating need for inhaled β-agonist therapy.

Why Write an Asthma Action Plan?

An action plan helps a patient to know what to do when an exacerbation occurs. National and international practice guidelines advocate partnerships between patients and health care professionals and recommend the use of written self-management plans.[7-9] Although there is no evidence that these written plans can prevent deleterious outcomes in asthma, the possible virtues of an action plan include reduced uncertainty for patients, less delay in securing necessary treatment, an earlier use of corticosteroid therapy for severe exacerbation, and a

*See also the editorial by R. E. Dales, MD, MSc, "Asthma Management—A Call for Action," on pages 157–158 of this issue.

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From the Department of Community Health Systems, University of California, San Francisco (UCSF), School of Nursing.
Reprint requests to Susan Janson, DNSc, RN, Dept of Community Health Systems, Box 0608, UCSF, San Francisco, CA 94143-0608.

possible reduction in the number of emergency department visits.

When patients are seen in follow-up, a review of the action plan in relation to recent asthma episodes can provide insight about a patient's ability to perceive declines in pulmonary function and effectively institute treatment. When a patient has managed an exacerbation appropriately, it is an occasion for reviewing achievement in self-management. Such reinforcement can promote continued efforts by the patient to adhere to needed daily therapy and enhance feelings of confidence in managing a chronic illness like asthma.[18–20]

Published guidelines for treatment often become community standards of care, especially when the disease is one, such as asthma, that is associated with substantial morbidity and mortality. When patients are informed about signs of increasing airflow obstruction and specific actions to take, they can be effective partners in their own health care.

When Should an Asthma Action Plan Be Written?

All patients with asthma need both verbal and written advice about signs that their asthma may be worsening and what actions to take at home. Initial plans should be provided at the time of the first visit in a clinician's office or at the time of discharge from an emergency department visit or hospital stay. The degree of detail in a plan depends on the patient's understanding and capabilities and on the severity of the patient's asthma. At a minimum, patients should be warned about key signs that asthma may be worsening and when to seek urgent care. Those who experience moderate to severe exacerbations or whose asthma is not under control may require written instructions about short-term changes in treatment. Patients who are capable of more complex self-management and those with more severe asthma need a detailed action plan to direct adjustments in treatment at home. Consultations between patient and health care professional about these adjustments can occur by phone or at the next follow-up visit.

Open communication between the physician and the patient will facilitate treatment and may enhance compliance.[21,22] Careful questioning about the most serious recent episode may elicit the information needed to assess a patient's understanding, skills, and need for more specific education or direction.

How Should Asthma Action Plans Be Written?

Controversy continues about the best method for writing an action plan. One uncontrolled study showed considerable improvement in clinical outcomes in a group of adults with asthma who followed a written peak flow–guided action plan.[12] In another study, substantial improvements in pulmonary function and bronchial responsiveness to histamine occurred in patients who self-adjusted treatment using a peak flow–directed plan, but no improvements were observed in controls.[10] Several studies have compared the use of peak flow–based action plans with one that is guided by symptoms only.[11,13,23] The most recent study showed that patients who were first educated and then used peak flow values to guide the therapeutic plan had fewer acute attacks, fewer days lost from work, and fewer emergency department visits than those who relied on symptoms and physicians' spirometry data.[14] Other investigators have shown no differences in outcomes between groups who used peak flow–based action plans and those who used an action plan based on changes in signs and symptoms; all patients improved substantially.[11,23] The results of these studies suggest that some sort of written plan, based on either symptoms or peak flow values, is better than no plan. According to one recent study, however, routine daily peak flow monitoring without an action plan apparently does little to improve outcomes.[24]

When contemplating whether to use symptoms, signs, and peak flow or a combination of these as a guide, it is helpful to remember that some patients may be poor perceivers of symptom severity.[25–27] The key warning signs of worsening asthma that patients should be educated about include the following[11,23]:

- An escalating need for bronchodilator medications;
- A shortened duration of medication effect, with the recurrence of symptoms within two hours after use;
- Waking at night or early morning with wheezing and difficulty breathing; and
- Important changes in the ability to engage in usual activities.

Instructions should be tailored for each patient and specific to allow the patient to adjust treatment according to a prearranged plan.

Because symptoms can be unreliable, practice guidelines recommend writing action plans based on peak flow measurements. Figure 1 is an example of such a plan.

Green Zone
80% to 100% of predicted or personal best peak flow
- Take your usual daily medications.

Yellow Zone
50% to 80% of predicted or personal best peak flow
- Use bronchodilator (2 puffs); recheck your peak flow in 20 minutes; if not improved, repeat 2 more puffs of bronchodilator.
- Other medications.

Red Zone
50% of predicted or personal best peak flow
- Medical alert! You need immediate treatment. Use your bronchodilator and call your doctor; if not available, go to the hospital right away.

If your bronchodilator lasts only 30 minutes or you have difficulty talking, go to the emergency department immediately!

Figure 1.—A sample asthma action plan based on peak flow is shown. See text for a more detailed description of the green, yellow, and red zones.

To use the zone system, the ranges must be calculated by a clinician and written out for each patient. The green zone means "all clear, continue as usual," and the variability of peak flow is usually less than 20% from night to morning. The yellow zone means "caution, action (medication) needed" because the peak flow is 50% to 80% of the patient's best value, and variability is 20% to 30%, often with increased signs and symptoms—nocturnal symptoms, coughing, wheezing, chest tightness with activity or at rest, and a decreased ability to engage in usual activities. Peak flow values in the yellow zone indicate an acute exacerbation, or a slow deterioration, of asthma that is not under good control. Increased doses or frequency of medication are usually needed. For certain patients, it has been recommended to divide the yellow zone into high yellow and low yellow zones to provide a more detailed and individually refined plan.[28] The red zone means "medical alert, urgent treatment needed," with the peak flow less than 50% of the patient's personal best. In this zone, asthma symptoms often are present at rest and greatly interfere with activity. Patients are instructed that lack of a prompt response to home treatment at this point means urgent medical care is needed, preferably at a hospital emergency department.

Other modifications of the three-zone plan are possible. Patients whose best peak flow is less than 300 liters per minute may benefit from a more conservative plan, with the green zone specified at 90% to 100% of the patient's best. Still others may not need to initiate treatment until the peak flow drops to 70% of the personal best. The action plan can be modified to meet the needs of each patient.

The plan need not be complicated or detailed if a patient has newly diagnosed asthma or has rare exacerbations. A simple directive may suffice about what to do if the patient wakes at night wheezing or has a peak flow below a specified critical level. For more experienced patients who are capable of self-managing and controlling their asthma, a specific set of instructions for the yellow zone may include increasing the doses of bronchodilator to two puffs every 20 minutes, repeating three times, and recording the peak flow value before and after each dose. After three such doses over the span of 60 minutes, the peak flow should return to the green zone or show a consistent upward trend. If it is not improving or is falling, the patient is instructed to call the clinician or to be seen for an evaluation. The British asthma guidelines also suggest another step: doubling the dose of the inhaled corticosteroid agent at a certain level of the peak flow, for example, at 70% of the best value or at the first signs of a developing cold.[29]

How Should Written Instructions Be Provided?

The action plan should be tailored for each patient. Whenever a written plan is provided to a patient, remember to document the written directives in the medical record to ensure continuity of care from other health care professionals who may interact with the patient. The following are examples of asthma action plans for patients with newly diagnosed asthma and asthma of varying severity:

Patient With Newly Diagnosed Asthma

Sheila is a 27-year-old secretary recently diagnosed with asthma that is not yet well controlled. She currently has symptoms during the day and seems frightened and overwhelmed by her diagnosis. Figure 2 shows a simple action plan that might be easiest for her to follow.

> Your asthma will improve slowly with regular and consistent use of your prescribed medications. But if you should notice that the effects of your inhaled bronchodilator [name of medication] do not last longer than 1 hour, and you are unable to perform your usual activities or to sleep because of symptoms, call your physician at [insert phone number] or come in to the office. If you have difficulty talking and breathing is becoming harder, go directly to the emergency department.

Figure 2.—A sample action plan is shown for patients with newly diagnosed asthma.

Mild Exercise-Induced Asthma

Jane, a 17-year-old competitive swimmer with asthma, says that her swim workouts are interrupted by wheezing. Figure 3 shows a simple preventive plan that might be adequate for her.

> 20 to 30 minutes before your exercise workout, take 2 puffs of your bronchodilator [name of medication]. Take 2 more puffs at the end of the workout if you are still wheezing. If your breathing does not improve with medication and rest and it is difficult to talk, call your physician at [insert phone number] or go to the emergency department.

Figure 3.—A sample action plan is shown for patients with mild, exercise-induced asthma.

Moderately Severe Asthma Well Controlled With Inhaled Steroid Therapy

Joe, a 40-year-old business executive, has had asthma for ten years. He began having daily symptoms about a year ago, requiring continuous treatment with daily inhaled corticosteroid and rescue inhaled β-agonist. Although his asthma is currently well controlled, he has occasional exacerbations with increased symptoms and had an emergency department visit a month ago. He will require a more detailed asthma action plan, such as shown in Figure 4.

Severe Steroid-Dependent Asthma

George is a 50-year-old businessman whose asthma

Green Zone

All clear. Your peak flow should be 80% to 100% of your personal best; for you, that is _____. You should not have symptoms that interfere with your sleep or usual activities. Take your regular daily medications as prescribed.

Yellow Zone

Caution! Your asthma has worsened and requires attention. Your peak flow may be 50% to 80% of your personal best; for you, that is _____. You may have been awakened from sleep with asthma symptoms and may not feel able to participate in your usual daily activities. Actions:

- Take 2 puffs of your bronchodilator [name of medication] now.
- Wait 20 minutes and check your peak flow. If not improved, take 2 more puffs of_____and repeat your peak flow.
- If not improved, repeat step 2. Your peak flow and your breathing should be improving, but if not, take the following medication [name of medication] and call [phone number].

Red Zone

Medical alert! You need immediate medical attention. Your peak flow is less than 50% of your personal best; for you, that is _____. Take 2 to 4 puffs of your bronchodilator [name of medication] plus [name of medication]. Go directly to the emergency department.

Figure 4.—A sample action plan is shown for patients with moderately severe asthma that is well controlled with inhaled steroid therapy.

has steadily worsened over the past six years despite maximal therapy. He now requires daily oral corticosteroid therapy in addition to daily inhaled steroid and β-agonist use. He has had about one emergency department visit in the past month for acute exacerbation. Figure 5 shows the asthma action plan that would be appropriate for such a patient.

Summary and Practical Tips for Writing and Using Action Plans

Written action plans help patients with asthma manage exacerbations at home or work. They may be written in a number of ways and tailored to each patient's personal profile. Although there is no evidence as yet that action plans can have an effect on asthma morbidity and mortality, several possible benefits have been reviewed. The following are practical suggestions for clinicians caring for persons with asthma to write effective action plans:

- Ask the patient what are the earliest signs of an asthma attack for him or her and how the symptoms typically progress. Use these to personalize the action plan.
- Teach the patient how to use a peak flow meter correctly, and check technique often. Compare trends in peak flow for an individual patient on the same brand of peak flow meter, if possible, because there is consistency only within a given brand.[29]
- Determine the patient's personal best peak flow after a trial of optimal therapy (consider a short course of prednisone). The patient's personal best may be more useful than the predicted value, but keep in mind that it can improve with optimal therapy or decline with fluctuations in the disease or substantial aeroallergen or toxic exposures. Use the personal best as the target goal to provide reinforcement. Use the predicted value if the personal best peak flow is not known.
- When a patient follows the plan appropriately, give lots of feedback and praise. Overall compliance often improves with direct positive reinforcement.
- Consider scheduling a "telephone consultation hour" when you are available for advice about implementing the written action plan. Instruct patients to measure their peak flow just before calling and have all current peak flow

Green Zone

Asthma stable. Your peak flow should be at or above this value:_____

- Take your usual daily medications as follows:

_____

_____

_____

High Yellow Zone (Mild Flare)

Your peak flow may have dropped to 70% to 90% of your usual best; for you, this is _____. Your symptoms may have worsened slightly. Actions:

- Take _____ puffs of your bronchodilator _____. Check your peak flow in 20 minutes. Your symptoms should be resolving, and your peak flow should be improving. If not, repeat _____ puffs of the bronchodilator and recheck your peak flow.
- You may repeat the above step twice. Symptoms should resolve, and peak flow should improve.

Low Yellow Zone (Moderate Flare)

Your peak flow may have dropped to 50% to 70% of your usual best; for you, this is _____. Your symptoms may have worsened substantially, and your sleep may be interrupted by asthma symptoms. Actions:

- Take _____ puffs of your bronchodilator [name of medication] and _____ puffs of the inhaled steroid [name of medication].
- Take _____ tablets of your oral steroid [name of medication].

Red Zone (Severe Flare)

Medical emergency!

- Take _____ puffs of your bronchodilator [name of medication], _____ tablets of your oral steroid, and go directly to the emergency department. If you are having trouble talking or walking, call 911 for immediate transport to the nearest hospital.

Figure 5.—A sample action plan is shown for patients with severe, steroid-dependent asthma.

information handy. Make sure the action plan has a phone number to call at any hour in an emergency.

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Commentary

Broken Promise

LAURENCE J. PURDY, MD, *Pomona, California*

Carol was a professor of philosophy and religious studies at a local university, where she taught ethics to undergraduates. I had read one of her books and felt fortunate when, through mutual friends, I had the opportunity to meet her. She was a big woman with large, deeply set, dark eyes and an acerbic wit that at first put me off. Once we became friends, however, it didn't take me long to notice that her sarcasm shielded her from the scrutiny of others and kept people at a safe distance. Through the opaque vision of my naiveté, I wondered what secret such an accomplished and successful woman would have that needed hiding from others, as if success or accomplishment were pillars of inner strength.

Though not a "full-blown manic-depressive," Carol in her more manic phases wore brightly colored dresses and makeup and occasionally tried a new hair style. At these times, she was humorous, or downright funny, as she reverently and irreverently mocked some of the peculiarities of Judaism, her focus of study and faith by heritage. Perhaps because of her many years of teaching, she spoke flawlessly and quickly, responding to questions in a way that always sounded rehearsed. In her more usual depressive phases, Carol dressed in a way that announced her mental state: somber brown and maroon shapeless dresses, sandals, and limp unwashed hair; her doughy face bespoke sleepless nights. A basically loving person, she believed strongly that she was loved by no one and would never be loved by anyone. This was her tormenting legacy from childhood, thick layers of a Dickensian tapestry of misfortune.

It was only after several years of friendship that Carol disclosed to me the nature of her underlying mental illness. She saw it as a powerful vortex that was dragging her down to a consequence that she had accepted long ago. At that point, had I been more callous, I would have prevented the friendship from developing further; I knew even then that it would be a difficult relationship and that I was setting myself up for a deep hurt. But our friendship did climb to a higher plateau. She eventually felt safe enough to reveal to me things I wasn't sure at first I really wanted to know, particularly the horror of her abusive childhood. She shared them with me in the way I imagine people do in confession. But I was not a link in her chain to God. Although Carol was a Judeo-Christian scholar who knew the Talmud by heart, she chose agnosticism as the most sensible way of viewing human existence. I will never know if this belief and its inherent nihilism played a part in her choice to end her life.

Over many a bottle of chardonnay, we talked. Rather, she talked and I listened to one sad tale after another. Her mother personified the wicked witch of folklore. The message she had received from her mother was that the universe had become a far sadder place after Carol's birth: "You're stupid; no one will ever love you. Look at you, go look in the mirror. How could anyone ever love an ugly bitch like you?" Then came the spitting in the face, the kicks when she lay on the floor wailing, and the silence in her lonely room, wondering what this was all about. The only truth a child knows comes from the lips of parents. A strong belief in her wretchedness was Carol's truth. It influenced all aspects of her life.

She once revealed that she had attempted suicide twice. Dress rehearsals, she jokingly called them. To me it was no joke. We talked about the famous suicides of writers, actors, and musicians, and I wondered what it must be like to have that much angst to disregard Hamlet's warning and annihilate oneself. Was there safety in darkness?

I have never before had a friend who committed suicide. Perhaps because I had always thought of myself as being cheerful and fun-loving, I never wanted to be associated with people who were outwardly depressed or moody. Always the teacher, though, Carol unknowingly taught me about her special types of secrets, the little devils that chip away at the firmament of the mind. Now that I have gone through life and the circle of my acquaintances has expanded, I realize that some of the people I have grown to like probably hide from me a dark corner of intense psychic pain that only shows itself privately. Perhaps there are many more such people than I can imagine. The masks we wear when we are around others are astounding.

Do people who suffer the way Carol did wonder if life is merely a prison from which escape is possible at any time? Does that knowledge give them solace? Do they ever consider another outlet for their pain? When the devils begin to jackhammer away at the integument

(Purdy LJ: Broken promise. West J Med 1996; 165:154-155)

From the Clinical Laboratory Medical Group, Pomona Valley Hospital Medical Center, Pomona, California.
Reprint requests to Laurence J. Purdy, MD, Clinical Laboratory Group, Pomona Valley Hospital, 1798 N Garey Ave, Pomona, CA 91767.

of sanity, is there a steam valve? Not even Sylvia Plath, who tried to exorcise her demons with lush poetry, could keep them away. Carol dove ever deeper into her work, but it never seemed good enough, as if some unseen authority were judging her. I watched as she worsened. One day I suggested we get together for lunch. "I'll call you," she said. "When I'm free." That day never came. The call I got was from a mutual friend who said that Carol was in the intensive care unit, ventilated, not yet brain dead, but not expected to improve. Her coma had become her refuge from the exigencies of life.

People don't kill themselves because a girlfriend left or because their performance on the job is poor or because of a divorce. Suicide is a dramatic volitional act that is the symbol of something dark and loathsome hiding deep in the psyche. The proximate event is merely the last straw of a set of life experiences that propel some people to their end. Carol believed she would never measure up to other people's expectations, not just in love, but in teaching, research, friendship—everything. It was painful for her to exist with this belief. As much as I wanted to help her and show her that I was a friend who would always be there for her, she also knew how hopeless and helpless she was.

At some point in our friendship, I had a strong feeling, just as she had, that her life would end this way. No matter how much we talked about it, no matter how many different medications she tried, and no matter how often she said she knew it, I could never convince her that I would be devastated if she were to die; she never thought her life could mean that much to others. Carol was not one to break a promise, so when she promised to call me if she ever again felt like killing herself, I felt relieved. But she broke her promise and is now in a coma on a ventilator.

Carol had enriched my life, but, sadly, the power of our friendship was no match to that of her depression. It is tragic to lose such a wonderful friend, but for her, I find myself curiously pleased. After a lifelong Sisyphean struggle against her psychic pain, she must have known she could never win. I would never want anyone to suffer as Carol had. When someone knows that the value of life is no longer worth the pain, whether psychic or somatic, it is time to let go. Had I been with her at the end, to hand her the wine to wash down the pills, it may have been the greatest moment we ever shared.

Editorials

Prognostic Factors and Management in Thyroid Cancer—Consensus or Controversy?

CARCINOMA OF the thyroid gland seems to defy many of the traditional rules of oncology. On the one hand, this cancer is often curiously indolent, and on the other hand, the staging systems of other epithelial cancers frequently fail when applied to thyroid cancer. Consequently, there has long been an interest in defining those factors that predict outcome in thyroid carcinoma, a topic that is aptly summarized by Orlo Clark, MD, in this issue of *The Western Journal of Medicine*.[1] Equally long-standing and extensive have been the efforts to define the optimal treatment of patients with thyroid cancer.

On first sight, it appears that the considerable efforts of the many investigators dealing with these questions have created a dense maze of contradictory and confusing data on both outcome prognostication and treatment approach. The histotype vies with the tumor grade, and patient age with tumor extent, for prognostic importance, and newer, more complex measurements on the molecular biologic level also seem to be relevant. On the treatment front, the battle is between local and radical tumor excision, selective versus extensive nodal dissection, the use of adjuvant radioiodine (RAI) therapy or not, and the use of suppressive or replacement thyroxine therapy. Much of this confusion undoubtedly stems from the absence of controlled trials in the management of thyroid carcinoma and from the fact that many medical specialties, from endocrinology to surgery to radiotherapy, are involved in the management of thyroid cancer. All involved have their own opinions on the optimal management, and confusion seems to reign. On closer inspection, however, there are more commonalities than differences, at least as far as staging is concerned.

The prognostic factors can be divided into host- and tumor-related factors. Among the host factors, all classification systems agree on the importance of age, with older patients doing worse, and to a lesser degree, sex, with male patients possibly doing worse than female patients. The most important tumor-related factors are also widely agreed on and are assessed with ease once the surgical pathologic report has become available. Not surprising and in agreement with all other human malignant neoplasms, the histotype is important. Within the most common histotypes, papillary and follicular thyroid carcinoma, the extent of tumor burden in the form of primary tumor size and local and distant spread is also generally agreed on as a major prognostic factor. These established host- and tumor-related risk factors predict most of the variation in thyroid cancer outcome, and the main difference between the various staging systems is in the weighing of individual factors. As a consequence, there is agreement in classifying patients into high-risk or low-risk categories. The overwhelming majority of patients are classified in the low-risk group, with the expected ten-year cause-specific mortality being less than 10%.

The strong consensus between staging systems on the basis of few, easily collected data has two consequences. First, without complex or expensive testing procedures, patients can be given a reasonably accurate prognosis following surgical therapy. Second, and possibly more important, it seems possible to sidestep a lot of the controversies surrounding treatment and follow-up once a patient's tumor has been staged. It seems illogical to submit the vast majority of patients who have a low risk of cancer death to extensive adjuvant treatment or follow-up, neither of which has proved to be beneficial. Although a number of retrospective studies suggest a possible small survival benefit of adjuvant RAI treatment, as many or more, though less often quoted, national and international studies have failed to support this notion.[2] Even if there was more retrospective evidence for the beneficial effects of RAI treatment, the observed magnitude of its effect in those studies supporting its use is so small that on a national basis, universal RAI use would save only a handful of lives per year at best, at considerable cost, inconvenience, morbidity, and the risk of possible long-term adverse effects to thousands of thyroid cancer patients. Given the first premise of medical practice, "do no harm," and the current medicofinancial climate, the most sensible approach seems to be to withhold adjuvant RAI treatment from most low-risk patients.

Similarly, suppressive doses of thyroxine might be reserved for high-risk patients, and follow-up in general may be less intense than traditionally taught for these persons. Most patients will require thyroxine replacement following an operation because primary surgery, as most often practiced, usually leaves little functioning thyroid tissue behind. Hence, the question of thyroxine replacement no longer is one of "if," but of "how much." As there is no published evidence linking suppressive doses (as defined by an undetectable serum thyroid-stimulating hormone [TSH] level measured by a sensitive assay) to improved survival, replacement or subsuppressive doses (serum TSH between 0.1 and 0.3 μIU per ml by sensitive assay) will probably suffice in most low-risk patients, while avoiding the possible side effects of long-term suppressive thyroxine therapy on heart and bone. Neither does it seem that the majority of these low-risk patients need extensive follow-up. In the absence of thyroglobulin autoantibodies, most of these patients can be observed by physical examination and serum thyroglobulin assays. Also, more than half of thyroid cancer recurrences and deaths occur within the first five years after primary therapy. Low-risk persons who have no evidence of recurrence at this stage will face a 10% to 15% lifetime risk of any recurrence thereafter, mostly in regional nodes, carry-

ing a low risk of subsequent further progression or death. The cost-effectiveness of intensive follow-up of these persons beyond five years must therefore be questioned.[2,3]

Thus, staging, though imperfect, can possibly simplify the management of a large proportion of thyroid cancer patients. Although sidestepping many of the controversies surrounding treatment, such an approach leaves essentially three areas of ongoing uncertainty and controversy. These are the extent of primary surgical treatment, the possible benefits of extensive nodal dissection, and the role of additional tumor-related factors in improving the predictive accuracy of "traditional" staging.

Incomplete tumor resection certainly impairs outcome, but there is no convincing evidence that more extensive primary surgical excision leads to improved outcomes, as long as the tumor resection was complete. In addition, as alluded to by Clark,[1] more extensive procedures are associated with increased complication rates. On the other hand, in recent years, reports have increasingly supported the benefits of total or near-total thyroidectomy over less extensive procedures, and in skilled hands, the complication rate can be low.[4] Moreover, this approach facilitates the use of any possible adjuvant RAI treatment as well as follow-up by increasing the reliability of serum thyroglobulin assays and postoperative diagnostic RAI scans. Therefore, if there is local surgical skill, and complication rates of near-total or total thyroidectomy are acceptably low, preference might be given to these procedures over less radical approaches.

By contrast, the value of extensive nodal dissection is less well supported. Reviewing the world literature, we neither found evidence for a substantial prognostic effect of nodal metastasis in differentiated thyroid cancer, nor were we convinced that extensive nodal dissection at presentation improves recurrence or death rates for nonmedullary thyroid carcinoma.[2,5] Nodal status should therefore not be considered a major factor in predicting thyroid cancer outcome or guiding primary treatment.

Some of the "newer," tumor-related risk factors unraveled over the past 10 to 15 years may eventually prove to be of importance in predicting the course of thyroid cancer and may even gain importance in the cytologic and histologic differential diagnosis of adenoma versus carcinoma. A number of oncogenes and tumor suppressor genes, as partially summarized by Clark,[1] have been implicated in thyroid cancer pathogenesis, but thus far they explain only a proportion of tumors and have not been unequivocally linked to prognosis. By contrast, cruder measures of differentiation and cytogenetic disarray, such as tumor grade and DNA ploidy, have been successfully linked to prognosis, suggesting that a multitude of genetic events occur during the transition of benign follicular cell to, first, well-differentiated and, later, poorly differentiated thyroid carcinomas. In follicular thyroid carcinoma, these events seem to involve predominantly the loss of genetic material, and deletions involving the short arm of chromosome 3 seem to be a frequent and possibly early occurrence.[6] Numerous other changes also occur, again reflecting the multistep nature of the process.

Future efforts to identify diagnostically and prognostically relevant molecular genetic events will have to focus on describing the molecular genetic changes occurring in tumor development as comprehensively as possible. The cytogenetic and molecular genetic tools for such a comprehensive genomic screening are now available in the form of comparative genomic hybridization,[8] representational difference analysis,[7] and other related techniques, and we probably can expect important advances in our understanding of the pathogenesis of thyroid cancer and further refinement of our prognostic scoring systems over the next decade.

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STEFAN K. G. GREBE, MD, FRACP
Visiting Scientist
Endocrine Research Unit

IAN D. HAY, MB, PhD, FRCP(Edin, Glasg & Lond)
Professor of Medicine
Mayo Medical School

Division of Endocrinology and Internal Medicine
Mayo Clinic
Rochester, Minnesota

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Asthma Management—A Call for Action

ASTHMA IS a chronic disease characterized clinically by variability in airflow obstruction over time. To manage asthma effectively, patients must recognize and avoid asthma triggers and inducers. A single exposure to an allergen may worsen asthma for several days to weeks.[1] Dust mites are an important risk factor for asthma worldwide.[2] Exposure to environmental tobacco smoke may be responsible for 20% of asthma symptoms in children.[3] Chronic asthma may develop in 5% of workers with exposure to isocyanates and will not resolve despite the cessation of the exposure.[4] Despite the avoidance of environmental agents that provoke asthma and the regular use of effective medications, severe exacerbations may

still occur. In children, viral infections may account for 85% of all severe exacerbations of asthma.[5] Although long-term asthma control can be achieved through environmental control and the regular use of effective medications, plans must be made for unavoidable acute exacerbations.

How do we wish patients to respond to worsening airflow obstruction? If an effective action plan is not formulated, then patients must rely on their natural tendencies. Some patients simply "tough it out" or "rest," but most increase the use of short-acting β-agonists.[6] In one study, 101 adults with asthma admitted to the Johns Hopkins Medical Institutions were interviewed to describe their outpatient management. During the 24-hour period before hospital admission, an average of 45 puffs from a metered-dose inhaler were taken.[7] These responses are inadequate. Apart from transient bronchoconstriction that readily responds to a short-acting bronchodilator, exacerbations are related to worsening airway inflammation that requires corticosteroid therapy.[8] In response to a scenario describing the rapid worsening of asthma, only 15% of patients with moderate to severe disease selected the appropriate time to increase the dosage of inhaled corticosteroids.[9] Inappropriate actions also delay further therapy. Audits of deaths from asthma have cited delays in corticosteroid use as an important fault.[10]

After a patient inhales large doses of β-agonists at home, the next stop is usually an emergency department. A population survey in Ontario, Canada, of 331,722 patients with asthma revealed that a third had visited an emergency department within the past 12 months.[11] On average, patients presented 4.4 days after symptom onset, at which time severe obstruction was present in 25%.[11] How effective is this plan of action? Like rescue inhalers, emergency departments offer an effective but transient solution. In British Columbia, 71 patients were contacted 12 days after discharge from an emergency department. Of these, 19 (27%) had returned to an emergency department and 43 (60%) continued to have symptoms.[12]

Elsewhere in this issue of the Journal, Susan Janson, DNSc, RN, explains that the purpose of an "action plan" is to instruct patients or family members how to adjust medication dosages to maintain good control of asthma.[13] Similar plans are an integral part of diabetes control, where blood glucose levels are monitored and insulin doses are adjusted by the patients. Action plans for asthma are not popular, however. If better guidance for the management of asthma exacerbations is not provided, we should not expect a better process or outcome than the current situation; yet, most patients have not discussed appropriate action plans with their physician. In the survey of hospitalized patients previously mentioned, only 28% had been given an action plan, and the usual plan is to go to an emergency department.[7] Similar results were obtained from a population survey of 2,342 Australian schoolchildren with "probable" asthma. Only 22% had an action plan.[14]

Why are action plans not prescribed more often? One reason may be that education is time-consuming. Another reason may be that the accumulating evidence of effectiveness is only now becoming convincing. Compared with traditional treatment, education and adjusting corticosteroid doses according to peak flow resulted in a 50% decrease in the number of physician visits, work absenteeism, and the use of antibiotics over a 12-month period in a Finnish study.[15] Another encouraging report from New Zealand describes community-based promotion of an action plan.[16] Physicians were informed and educated, and then action plans were advertised and disseminated to patients through physicians' offices, pharmacies, and the local asthma society. Patients were asked to bring their plans to their usual physician for completion (personalization). Effectiveness was evaluated by interview a few months afterwards. Of the 109 patients with a completed plan, most felt more confident about self-management, and the incidence of nocturnal waking lessened. The emergency use of nebulizers did not measurably decrease. Although the data were not presented, the power of this study to detect a substantial reduction in emergency visits would have been low given the sample size, expected frequency of emergency visits, and the short interval between intervention and follow-up.

Another reason for the infrequent use of action plans may be the difficulty involved in writing an effective plan. Take the example of the action plans described by Janson in this issue.[13] The sample action plan based on peak flow could result in the frequent use of inhaled bronchodilators if peak flows remained between 50% and 80%. Even when flows are less than 50%, there is no recommendation for the use of either inhaled or oral corticosteroids, the definitive treatment. A patient with this plan may remain at home, overusing the rescue inhaler until airway inflammation has progressed to the point of severe obstruction. A helpful addition would be to double or triple the dose of inhaled corticosteroids when the peak flow after bronchodilator use falls below 75% or 80% and to start taking prednisone when it falls below 60%.[17]

Criticism is hard to justify, however, given that there is little empiric evidence to guide the preparation of an action plan. When should the use of inhaled corticosteroids and prednisone be started or increased, and in what doses? Surely these must be a function of the underlying asthma severity, the degree of worsening, and how quickly the lung function is deteriorating. Clinical research in this area could have great practical value. There is even controversy regarding the usefulness of peak flow monitoring. Until more information is forthcoming, a suggested compromise is to use peak flow monitoring in patients who poorly perceive airflow obstruction and in those with severe asthma.[18]

What should be done to promote the use of action plans? Janson's article serves to remind and educate the medical community about action plans.[13] Research is needed to determine the characteristics of the plan, the patient, and the patient's asthma that are associated with effectiveness. Meanwhile, several action plans have been

described, at least one of which appears to be highly effective.[15] Publicizing the concept of asthma self-management in the medical literature and in the lay press will, I hope, prompt physicians and patients to initiate discussions. The repeated call that "Patients with asthma must become effective partners in their own care"[19] has not been heard. Although much remains to be known about action plans, the alternative, continuing to overuse β-agonists and emergency departments, is dangerous, depletes health care dollars, and provides only short-term relief.

ROBERT E. DALES, MD, MSC
Departments of Medicine and Epidemiology and Community Health
University of Ottawa Faculty of Medicine
Ottawa, Ontario, Canada

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The Order of the Day? Cheers, Thanks, and Introductions

It was a cliffhanger. But we made it. *The Western Journal of Medicine* didn't die. Why not? Shared vision, teamwork, grit, good luck, perseverance, and optimism. In short: keeping on keeping on in pursuit of excellence. In June, I described the journal's history, survival saga, and some of the key people whose inspiration and devotion meant everything.[1] This is the time and place for cheers and thanks . . . and introductions.

Carden Jennings Publishing Company, Ltd, a rapidly growing publisher of scientific journals based in Charlottesville, Virginia, is the new publisher of *The Western Journal of Medicine*. The California Medical Association will retain control of the journal's editorial content and direction. The President of Carden Jennings, Bill Carden, has said, "We will maintain the high standards of editorial excellence for the journal while striving to enhance the reach, influence, and appearance beyond its current level." Carden Jennings will develop Internet links to support these goals and to ease communications with *WJM's* subscribers and authors. In addition to the journal, Carden Jennings publishes scientific and medical journals, books, proceedings, newsletters, and multimedia CD-ROMs and has an Internet presence as well. The range of publications includes primary care, cardiology, diabetes, hematology, oncology, bone marrow transplantation, and the radiation sciences. Although change is challenging, the downright basic niceness and intelligence of the Carden Jennings staff, coupled with Bill Carden's philosophy, "All things are possible," combined with extraordinary efforts on the part of California Medical Association and *WJM* staff members, are making the change collegial and full of hope. The future looks bright as we move toward achieving financial stability and have the opportunity to develop and improve the *Journal's* fundamental mission to apply science to the bedside and provide physicians with the most current practice and policy information.

The new associate editor of *The Western Journal of Medicine* is Edward D. Harris Jr, MD. Dr Harris's tenure starts October 1st following the retirement of Lloyd Hollingsworth Smith Jr, MD, who honored the journal by his 28 years of service. Dr Harris attended Harvard Medical School and had his internal medicine and clinical research fellowships (rheumatology) at the Massachusetts General Hospital. After serving on the faculty at Harvard, he became Professor of Medicine at the Dartmouth-Hitchcock Medical Center and later was the Chair of Medicine at UMDNJ-Rutgers Medical School and at Stanford University School of Medicine. He is currently the George DeForest Barnett Professor of Medicine at Stanford, where he directs the Center for Musculoskeletal Diseases. Dr Harris is a noted editor and author whose book, *Rheumatoid Arthritis*, will be published next year by W. B. Saunders. The book is meant for clinical investigators, rheumatologists in practice and training, internists, and other primary care physicians. Dr Harris also

has served the scientific community through his work with the American College of Rheumatology, the Arthritis Foundation, the American Board of Internal Medicine, the American College of Physicians, the Association of Professors of Medicine, and a variety of federal scientific study groups and advisory boards as well as industry and academic associations. He is a sought-after lecturer, president-elect of the Medical Staff at Stanford University Hospital, and President of the California Academy of Medicine. He will bring great energy, wisdom, and a welcome continuation of wit to the *Journal* and its readers.

Over the last year, the *Journal* has had a tough climb. We are at a new peak. We look forward to serving medicine, our patients, and the public. We pause, now, briefly, to cheer and thank you and others who have worked so hard on the ascent and to welcome with firm handshakes new partners and colleagues. See you next month.

LINDA HAWES CLEVER, MD
Editor

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Correspondence

Female Prostatitis?

To the Editor: Ruben F. Gittes, MD, and Robert M. Nakamura, MD, are to be congratulated for calling attention to the urethral syndrome, perhaps the commonest urologic complaint among female office patients.[1] In fact, the figure cited of 5 million office visits annually seems far too conservative. The authors propose to attribute the urethral syndrome to infection in distal paraurethral glands ("the female prostate") based on the following factors:

- Palpation tenderness of these paraurethral sites,
- Symptomatic improvement with antibiotic treatment,
- A proposed analogy with male prostatitis, and
- Histologic inflammation in a single necropsy specimen.

Several issues are raised that question the validity of this concept, beginning with the culture-negativity of urine and urethral expressions that epitomize this syndrome. Palpation tenderness resolving with antibiotic therapy is persuasive, but another feature of the urethral syndrome must be considered—namely, a tendency for symptoms to evanesce, waxing and waning without apparent provocation. Also, patients often describe improvement during antibiotic therapy, only to have prompt recurrence on the withdrawal of therapy. Moreover, to support this concept by citing the common practice of diagnosing prostatitis based upon digital rectal tenderness without laboratory substantiation ignores the condemnation of that practice as unjustified and leading to a gratuitous waste of resources. Finally, the histologic specimen included in the report lacks any information supporting a clinicohistologic connection: this example is specious if it cannot be stipulated that the patient suffered from the urethral syndrome.

The authors refer to urethral dilatation as both condescending and not beneficial. In my experience, physicians who denounce urethral dilatation routinely underdilate, in which case benefit is absent or temporary. A caliber of 38F in adults is necessary, and mild, temporary urethral bleeding is a favorable prognostic sign. Relief is typically prompt. Benefit is reflected in the patients who voluntarily return after varying intervals for retreatment when symptoms recur. The second dilation is seldom as uncomfortable as the first.

Gittes and Nakamura may be correct in their observation, but substantiation is necessary before the expense involved in the therapy they advocate can be considered. In pursuit of this theory, they may wish to consider two intriguing factors:

- The urinary sediment of patients with the urethral syndrome characteristically contains a large number of squamous epithelial cells, as does the urine of men receiving estrogen therapy (for prostate cancer);
- Patients with the urethral syndrome and no manifestations of estrogen deprivation often benefit symptomatically from exogenous estrogen therapy; male patients with symptomatic benign prostatic hypertrophy have benefited (subjectively) from similar therapy.

NORMAN E. PETERSON, MD
Chief, Division of Urology
Denver Health Medical Center
777 Bannock St
Denver, CO 80204-4507

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To the Editor: Regarding the article on the female urethral syndrome by Ruben Gittes, MD, and Robert Nakamura, MD, some of the women we see with nonspecific symptoms and no demonstrable infection by standard culture definitely need a trial of antibiotic therapy (my choice is doxycycline) before we proceed with cystoscopy to rule out interstitial cystitis.

Likewise, from the standpoint of the male so-called nonbacterial prostatitis, a few urologists in our community are evaluating these cases for possible interstitial cystitis. Several male patients whom I have taken the trouble to cystoscope under anesthesia and dilate have had definite glomerulations. Indeed, they have substantial abatement of symptoms simply from bladder dilation.[1]

Obviously, we still have a lot to learn.

M. FRANCIS RUSSI, MD
Division of Urology
Good Samaritan Medical Group
2585 Samaritan Dr
San Jose, CA 95124

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Jarisch-Herxheimer Reaction

To the Editor: I read with interest the article by Judy L. Flores, MD, on the treatment of syphilis,[1] but the author failed to mention an important clinical phenomenon that all clinicians caring for patients with syphilis should be aware of: the Jarisch-Herxheimer reaction. This is a systemic febrile reaction occurring in about 60% of patients treated with penicillin for syphilis.[2] It was described by

Jarisch, Herxheimer, and Krause at the turn of the century, but was initially noted in the 15th century when topical arsenic was first used to treat syphilis.[3] The reaction, typically occurring 6 to 12 hours after therapy for syphilis is initiated, consists of fever, rigors, malaise, diaphoresis, and an exacerbation of preexisting cutaneous lesions.[3,4] The Jarisch-Herxheimer reaction is more annoying than dangerous to patients, although on rare occasions patients with neurosyphilis may experience seizures, monoplegia, or hemiplegia.[4] Another possibly dangerous outcome, although rare, is inflammation of the aorta or coronary ostia in patients with cardiovascular involvement.[2,4]

The cause of the Jarisch-Herxheimer reaction is thought to be due to the death of spirochetes, which liberates toxins from the organism.[4] Early studies postulated that dying treponemes released an endotoxin similar to that of gram-negative organisms.[4] Subsequent investigators have convincingly demonstrated, using the limulus amebocyte lysate test in humans and in rabbits, that endotoxin is not released by treponemes.[5] Young and coworkers assayed serum specimens before, during, and after treatment of syphilis in 19 patients, and all specimens were negative for endotoxin. They also were able to reproduce a syndrome similar to the Jarisch-Herxheimer reaction after treatment with penicillin in rabbits infected with *Treponema pallidum* and were not able to recover endotoxin.[5] The exact cause is not precisely known, but could relate to the formation of immune complexes triggered by antigen release from dying spirochetes.[2,5]

Reactions similar to the Jarisch-Herxheimer reaction may occur in other infections, including borreliosis, brucellosis, and trypanosomiasis.[5] The Jarisch-Herxheimer reaction is typically more severe in relapsing fever (borreliosis) and may include hypotension, a decrease in cardiac output, and lactic acidosis.[4,5] Fortunately, the reaction in the treatment of syphilis is rarely of this degree and usually subsides spontaneously. Clinicians should not confuse the Jarisch-Herxheimer reaction with a penicillin allergy as this is the drug of choice. Furthermore, the onset of the reaction after treatment with penicillin may provide a clue to undiagnosed syphilis in a patient treated with penicillin for another reason.[4]

MARK A. MARINELLA, MD
Wright State University
School of Medicine
Dayton, OH 45429

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Lessons From the Practice

The Extra Window

LANCE MONTAUK, MD, *Berkeley, California*

While attending in a university hospital emergency department, I was asked by house staff to listen to a patient's heart. The patient, a Cambodian immigrant in his early 20s, was complaining of fever and mild shortness of breath. The residents said he had a loud murmur, and they wondered if I could tell them what it was. I asked about his medical history, but they said he did not communicate well.

The patient, of slight build, was sitting on a gurney with two friends nearby. I exchanged a few words with him, and he responded in simple but appropriate English. When I put my stethoscope to his chest, the thrill vibrated halfway up my arm. It was so powerful that I was surprised that I had not heard it with the unassisted ear when standing close to the patient. It was mainly systolic and covered his entire anterior left chest wall, but heard loudest over the left sternal border. Was it merely resonating into diastole, or was that a separate component? No, it seemed not to change with the respiratory cycle. Would it help to have the patient squat or lean forward?

I looked at the patient while listening. Was he slighter than his comrades? Had he borne this thrill since birth? Was it diminished—or even reversed—by increasing right-sided pressures? How could I find out and be the resource my house staff desired?

"Your heart has an unusual sound," I told the young man.

"I know," he replied.

"Have you ever seen a doctor about it before?"

"Yes, in Thailand, before I came to America."

"What did the doctor there say it was?"

"He asked my heart questions, and it answered with pictures, but I cannot explain in English," he answered hesitantly.

"How did he ask the questions?" I inquired.

"He rubbed jelly on my chest and sent the questions to the heart with the same sounds we use to talk."

"And how did the heart answer?" I pursued. "Try to tell me."

He paused. "The doctor said that a heart has four rooms. Two of the rooms have a door between them, and they are filled with red blood. The other two rooms have a door between them, but they are filled with black blood. My heart has an extra window in it, between the rooms with the red blood and the black blood, and the red blood goes through the window into the black blood."

I thanked the young man for the description of his problem and told the staff that echocardiography of the young man would probably reveal a ventricular septal defect.

(Montauk L: The extra window. West J Med 1996; 165:163)

From the University of California, San Francisco (UCSF), Division of Emergency Medicine. Dr Montauk is an attending physician at California Pacific Medical Center, San Francisco.

Reprint requests to Lance Montauk, MD, 3033 Bateman St, Berkeley, CA 94705-2507.

Selective Deafness

SIMON AUSTER, MD, JD, *Bethesda, Maryland*

At 73 years old, still with a full head of thick, salt-and-pepper hair, his patrician features unmarred by wrinkles, the patient was a sturdy survivor of three serious myocardial infarctions. This was his fifth admission to the coronary care unit (CCU), another "R/O MI." This time, it turned out, he had merely severe angina. If not for CCU visiting rules, he would have been surrounded by his attentive family who spent most of the day in the visitors' area. His wife, eight years his junior but in appearance ten years his senior, was diabetic and nearly blind, and her anxiety about his illness was poorly contained. She was constantly seeking reassurance, from their children, from the nurses, and from me, the resident caring for him. She also, indirectly, sought reassurance from the patient, asking him how soon he would be coming home to take care of all of the things that had gone wrong since he had become ill.

Shortly before his discharge, I was approached by one of his daughters. His children were aware of the pressure their mother was unwittingly placing on their father in her frantic casting about for reassurance. They were concerned about the effect this might have on their father when he returned home. They feared he would overexert himself in an effort to assuage his wife's anxiety. To extend his convalescence, the children had agreed among themselves to invite their parents to stay with any one of them for several weeks following his discharge. But their father was adamant; he and his wife belonged at home, and that was where he was going.

Would I help? Would I persuade their father to go with one of them? I hesitated. Through the misadventures to which the naive are prone, I had learned to be cautious about being drawn into such family discussions without having a reasonable appreciation of how the family operated. Yet, despite their almost continuous presence, I really had no sense of how this family functioned. But they were clearly a caring family, so, albeit with some reluctance, I agreed.

My initial approach was upbeat: "Wouldn't it be nice to get away for a while and see the grandchildren?"

"No, Doctor, my place is at home with Mama."

I rattled the medical saber a little: "It will help your recovery to be able to rest for a while longer."

"No, Doctor, my place is at home with Mama."

I indulged in a little clinical sniping: "It's hard to rest when you go home, and there are things to do all around."

"No, Doctor, . . ."

At this point, it had become a challenge to my persuading abilities, and I pulled out the big guns: "But when you're at home, your wife is always pressing you to do things, and it's not good for you to be under so much pressure."

At that, this distinguished, courtly gentleman turned and looked directly at me with the pitying look I could imagine he would use with a child. "But, Doctor, you don't have to worry. I don't listen."

Caution in intervention, whatever its nature, is a lesson that often needs to be relearned.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

(Auster S: Selective deafness. West J Med 1996; 165:164)

From the F. Edward Hébert School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland.

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Reprint requests to Simon Auster, MD, JD, Uniformed Services University of the Health Sciences, A-1038, 4301 Jones Bridge Rd, Bethesda, MD 20814-4799.

In Memoriam

California Medical Association

Birch, Ronald Stuart, Sacramento. Died May 24, 1996, aged 71. Graduate of University of California, San Francisco, School of Medicine, 1951. Licensed in California in 1951. Dr Birch was a member of the Sacramento–El Dorado Medical Society.

Chapman, Ethel A., San Bernardino. Died Aug 21, 1996, aged 87. Graduate of Loyola University Medical School, 1934. Licensed in California in 1956. Dr. Chapman was a member of the San Bernardino Medical Society.

Conforth, Elizabeth L., San Diego. Died July 26, 1996, aged 60. Graduate of Creighton University School of Medicine, 1963. Dr. Conforth was a member of the San Diego Medical Society.

Curry, Francis, San Francisco. Died Aug 3, 1996, aged 85. Graduate of Stanford University School of Medicine, 1946. Dr Curry was a member of the San Francisco Medical Society.

Dunford, Ruth, Bakersfield. Died Aug 23, 1996, aged 77. Graduate of University of Iowa School of Medicine, 1943. Licensed in California in 1946. Dr Dunford was a member of the Kern Medical Society.

George, Ralph P., San Diego. Died Jun 2, 1996, aged 87. Graduate of the University of Minnesota, 1932. Dr. George was a member of the San Diego Medical Society.

Green,Walter, San Francisco. Died Aug 7, 1996, aged 70. Graduate of University of Michigan School of Medicine, 1953. Dr Green was a member of the San Francisco Medical Society.

Kaufman, Paul, San Francisco. Died Jun 15, 1996, aged 67. Graduate of Stanford University School of Medicine, 1953. Dr Kaufman was a member of the San Francisco Medical Society.

Kelenscher, Alan J., Sacramento. Died July 29, 1996, aged 70. Graduate of NY University College of Medicine, 1949. Licensed in California in 1959. Dr Kelenscher was a member of the Sacramento–El Dorado Medical Society.

Kirklin, Ashley R., San Francisco. Died July 21, 1996, aged 73. Graduate of Temple University School of Medicine, 1946. Dr Kirklin was a member of the San Francisco Medical Society.

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Morel, J. Felix, Napa. Died Jun 8, 1996, aged 71. Graduate of Louisiana State University, 1953. Dr Morel was a member of the Napa Medical Society.

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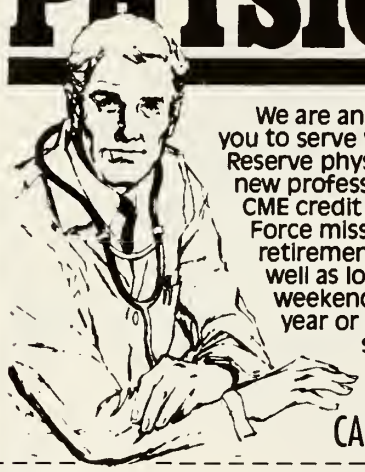

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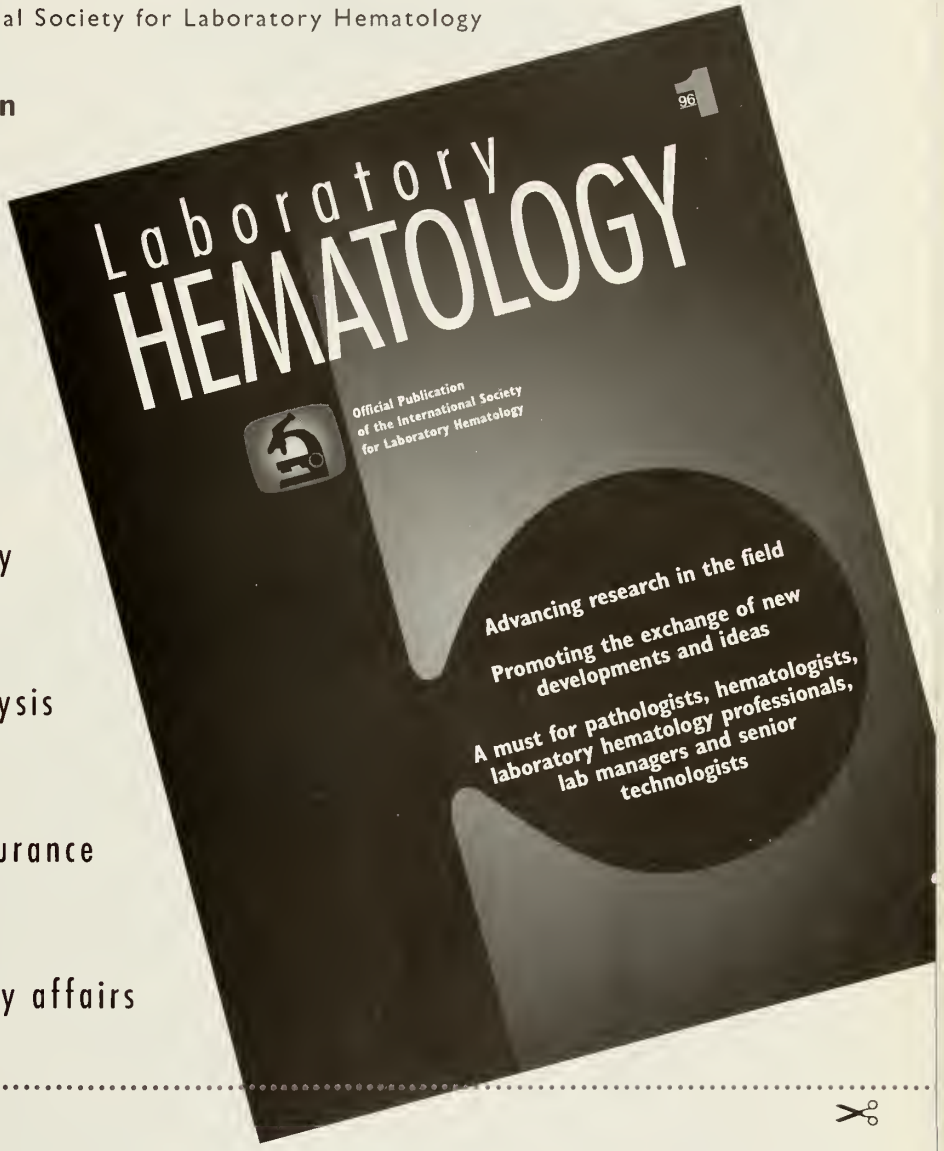

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Advertising Index

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Biology of Blood & Marrow Transplantation 175

BloodLine . . . . . 3rd Cover

Laboratory Hematology 174

DELANO REGIONAL HOSPITAL 173

NORCAL MUTUAL INSURANCE COMPANY 99

PRIME CLINICAL . . . . . 4th Cover

PRUDENTIAL HOME MORTGAGE 101

SMITHKLINE BEECHAM

Augmentin . . . . . 2nd Cover, 97

UCLA, SCHOOL OF MEDICINE,
DIVISION OF GERIATRICS 101

UNIVERSITY BOOKSTORE

Encyclopedia of Cancer. 111

THE WESTERN JOURNAL OF MEDICINE

Coming in the October Issue 173

Special Issues Catalog 105

WJM Subscription Order Form. 103

wjmed.com 107, 173

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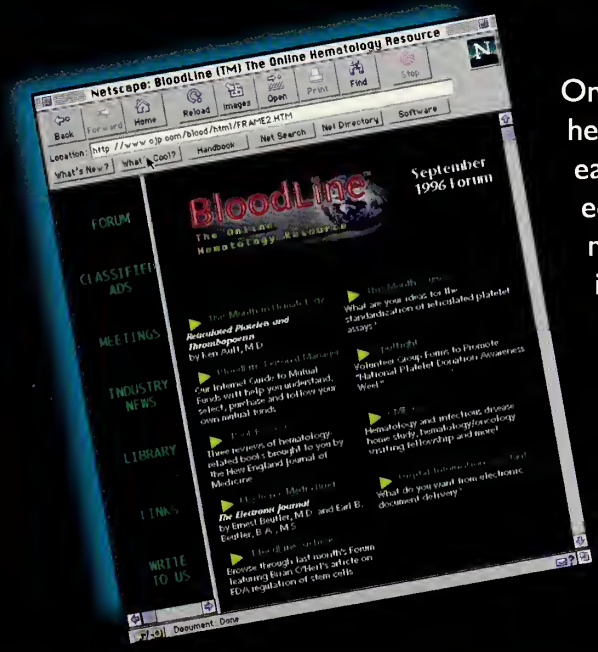

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The Western Journal of Medicine

VOLUME 165 • NUMBER 4 OCTOBER 1996

ARTICLES

192 Surveillance of Traumatic Brain Injuries in Utah
D J THURMAN, L JEPPSON, C L BURNETT, D E BEAUDOIN, M M RHEINBERGER, and J E SNIEZEK

197 Sputum Gram's Stain in Community-Acquired Pneumococcal Pneumonia
W W REED, G S BYRD, R H GATES Jr, R S HOWARD, and M J WEAVER

205 When Patients Ask About Assisted Suicide—A Viewpoint From Oregon
M A LEE, L GANZINI, and K BRUMMEL-SMITH

209 Practice Environment for Nurse Practitioners in California—Identifying Barriers
A L ANDERSON, C L GILLISS, and L YODER

CONFERENCES AND REVIEWS

215 Prognosis and Treatment of Burns
R MANN and D HEIMBACH

EPITOMES

221 Important Advances in Preventive Medicine and Public Health

ALERTS, NOTICES, AND CASE REPORTS

229 Spontaneous Group B Streptococcal Meningitis in a Patient With Cirrhosis
B Y TUNG and K V KOWDLEY

231 Lysinuric Protein Intolerance Presenting as Coma in a Middle-Aged Man
M GARE, M SHALIT, and A GUTMAN

TOPICS IN PRIMARY CARE MEDICINE

234 Parkinson's Disease—Diagnosis and Treatment
D C NG

COMMENTARY

241 Academic Physicians, Clinical Investigators, and Managed Care—Whither Hippocrates?
W M BENNETT

EDITORIALS

245 Barriers to Practice—Reality or Perception?
K M TAIT and R J PATCHIN

246 Physicians and Nurse Practitioners—Old Conflicts and New Opportunities
L J FINOCCHIO, J M COFFMAN, C M DOWER, and E H O'NEIL

248 Parkinson's Disease—A Progress Report
M J AMINOFF

250 A Guide of the Perplexed—Assisted Suicide
A R JONSEN

CORRESPONDENCE

252 Out-of-Control Snowboarders • Response

LESSONS FROM THE PRACTICE

253 I Owe It All to Jose and His Mother
E T MATTHEWS

254 Myopia Revisited
S M CHEN

OTHER FEATURES

183 Subscription Information

186 Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming

204 Poem

255 In Memoriam

256 Instructions for Authors

258 Business and Subscription Information

260 Classified Advertising

264 Western State Medical Associations' Meetings

Detailed Table of Contents: 180, 182, 184

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Bacteriological studies to determine the causative organisms and their susceptibility to *Augmentin* should be performed together with any indicated surgical procedures. Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once results are known, adjust therapy, if appropriate.
CONTRAINDICATIONS: Patients with a history of allergic reactions to any penicillin, or patients with a history of *Augmentin*-associated cholestatic jaundice/hepatic dysfunction.
WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH *AUGMENTIN*, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.** Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic associated colitis." After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis. Use *Augmentin* cautiously in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with *Augmentin* use is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. (See CONTRAINDICATIONS and ADVERSE REACTIONS.)
PRECAUTIONS: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.
A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.
Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin. Co-administration of probenecid cannot be recommended. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.
Drug/Laboratory Test Interactions: Oral administration of *Augmentin* will result in high urine concentrations of amoxicillin. High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin and therefore *Augmentin*, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Tes-Tape®) be used.
Following administration of ampicillin to pregnant women a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone and estradiol has been noted. This effect may also occur with amoxicillin and therefore *Augmentin*.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. **Mutagenesis:** The mutagenic potential of *Augmentin* was investigated *in vitro* with an Ames test, a human lymphocyte cytogenetic assay, a yeast test and a mouse lymphoma forward mutation assay, and *in vivo* with mouse micronucleus tests and a dominant lethal test. All were negative apart from the *in vitro* mouse lymphoma assay where weak activity was found at very high, cytotoxic concentrations.
Impairment of Fertility: *Augmentin* at oral doses of up to 1200 mg/kg/day (5.7 times the maximum human dose, 1480 mg/m²/day, based on body surface area) was found to have no effect on fertility and reproductive performance in rats dosed with a 2:1 ratio formulation of amoxicillin/clavulanate.
Teratogenic effects: Pregnancy (Category B): Reproduction studies performed in pregnant rats and mice given *Augmentin* at oral dosages up to 1200 mg/kg/day, equivalent to 7200 and 4080 mg/m²/day, respectively (4.9 and 2.8 times the maximum human oral dose based on body surface area), revealed no evidence of harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.
Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.
Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.
ADVERSE REACTIONS: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were mild and transient, <3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include abdominal discomfort, flatulence and headache.
The following adverse reactions have been reported for ampicillin class antibiotics:
Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis, mucocutaneous candidiasis and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.) Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome) and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis). These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin. (See WARNINGS.) A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. Interstitial nephritis and hematuria have been reported rarely. Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*. Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.
DOSAGE AND ADMINISTRATION
Since both the *Augmentin* 250 mg and 500 mg tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), 2 *Augmentin* 250 mg tablets are not equivalent to 1 *Augmentin* 500 mg tablet. Therefore, 2 *Augmentin* 250 mg tablets should not be substituted for 1 *Augmentin* 500 mg tablet.
Dosage:
Adults. The usual adult dose is 1 *Augmentin* 500 mg tablet every 12 hours or 1 *Augmentin* 250 mg tablet every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be 1 *Augmentin* 875 mg tablet every 12 hours or 1 *Augmentin* 500 mg tablet every 8 hours.
Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with a glomerular filtration rate of <30 mL/minute should not receive the 875 mg tablet. Patients with a glomerular filtration rate of 10 to 30 mL/minute should receive 500 mg or 250 mg every 12 hours, depending on the severity of the infection. Patients with a less than 10 mL/minute glomerular filtration rate should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection.
Hemodialysis patients should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection. They should receive an additional dose both during and at the end of dialysis.
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals. (See WARNINGS.)
Pediatric Patients: Pediatric patients weighing 40 kg or more should be dosed according to the adult recommendations.
Due to the different amoxicillin to clavulanic acid ratios in the *Augmentin* 250 mg tablet (250/125) versus the *Augmentin* 250 mg chewable tablet (250/62.5), the *Augmentin* 250 mg tablet should not be used until the pediatric patient weighs at least 40 kg or more.
Administration: *Augmentin* may be taken without regard to meals, however, absorption of clavulanate potassium is enhanced when *Augmentin* is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, *Augmentin* should be taken at the start of a meal.
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VOLUME 165 • NUMBER 4 • OCTOBER 1996

CONTENTS

ARTICLES

192 **Surveillance of Traumatic Brain Injuries in Utah**

DAVID J. THURMAN, MD, MPH; LEW JEPPSON, MS; CINDY L. BURNETT; DENISE E. BEAUDOIN, MD, MSPH; MARGUERITE M. RHEINBERGER, JD, MPH; and JOSEPH E. SNIEZEK, MD, MPH

From the National Center for Injury Prevention and Control, Centers for Disease Control and Prevention, Atlanta, Georgia; and the Division of Community and Family Health Services, Utah Department of Health, Salt Lake City.

197 **Sputum Gram's Stain in Community-Acquired Pneumococcal Pneumonia—A Meta-analysis**

LTC WILLIAM W. REED, MPH, MC, USA; GREGORY S. BYRD, MD; COL ROBERT H. GATES, Jr, MC, USA; ROBIN S. HOWARD, MA; and MICHAEL J. WEAVER, MD

From the Department of Medicine, Fitzsimmons Army Medical Center, Aurora, Colorado, and the Department of Clinical Investigation, Walter Reed Army Medical Center, Washington, DC.

205 **When Patients Ask About Assisted Suicide—A Viewpoint From Oregon**

MELINDA A. LEE, MD; LINDA GANZINI, MD; and KENNETH BRUMMEL-SMITH, MD

From the Departments of Medicine, Psychiatry, and Family Medicine, Oregon Health Sciences University; the Gerontology Section and Geriatric Psychiatry, the Medical and Psychiatry Services, Veterans Affairs Medical Center; and the Division of Long-Term Care, Providence Health Systems, Portland, Oregon.

209 **Practice Environment for Nurse Practitioners in California—Identifying Barriers**

ARLYSS L. ANDERSON, MHS, RN,CS, FNP; CATHERINE L. GILLISS, DNSc, RN,CS, FAAN; and LAURIE YODER, MN, MPH, RN,CS, FNP

From the Department of Family Health Care Nursing, University of California, San Francisco, School of Nursing.

CONFERENCES AND REVIEWS

215 **Prognosis and Treatment of Burns**

ROBERTA MANN, MD, and DAVID HEIMBACH, MD

From the Department of Surgery, University of Washington School of Medicine, and the Burn Center, Harborview Medical Center, Seattle.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Preventive Medicine and Public Health

Items of progress in preventive medicine and public health. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

221 **Epidemiology and Control of Coccidioidomycosis in California**

GEORGE W. RUTHERFORD, MD, and MARK F. BARRETT

222 **Occupational Lead Exposure and Management**

JAMES P. SEWARD, MD, MPP

224 **Human Babesiosis and Ehrlichioses—Emerging Tick-Borne Diseases**

DUC J. VUGIA, MD, MPH, and VICKI L. KRAMER, PhD

(Continued on Page 182)

"Being a doctor has allowed me to provide the best for my family."

DR. JANELLE GOETCHEUS, MEDICAL DIRECTOR, HEALTH CARE FOR THE HOMELESS PROJECT, INC., WASHINGTON, DC

Dr. Goetcheus says that raising her children in a health recovery facility for the homeless is one of the greatest gifts she has given them.

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(Continued from Page 180)

224 **Directly Observed Therapy for Tuberculosis**
ELIZABETH MANNINO, MD, MPH, and LINDA HILL, MD, MPH

225 **Multidrug-Resistant Tuberculosis—How Far Are We From New York City?**
ANNETTE NITTA, MD

226 **Smoking Cessation—New Challenge and Opportunities**
BRUCE N. LEISTIKOW, MD, MS

227 **Naltrexone Hydrochloride Use in the Treatment of Alcoholism**
STEVEN R. EY, MD

ALERTS, NOTICES, AND CASE REPORTS

229 **Spontaneous Group B Streptococcal Meningitis in a Patient With Cirrhosis**
BRUCE Y. TUNG, MD, and KRIS V. KOWDLEY, MD
From the Division of Gastroenterology, Department of Medicine, University of Washington School of Medicine, Seattle.

231 **Lysinuric Protein Intolerance Presenting as Coma in a Middle-Aged Man**
MEIR GARE, MD; MEIR SHALIT, MD; and ALISA GUTMAN, MD
From the Division of Internal Medicine, Hadassah University Hospital, Jerusalem, Israel.

TOPICS IN PRIMARY CARE MEDICINE

234 **Parkinson's Disease—Diagnosis and Treatment**
DON C. NG, MD
From the Division of General Internal Medicine, University of California, San Francisco, School of Medicine.

COMMENTARY

241 **Academic Physicians, Clinical Investigators, and Managed Care—Whither Hippocrates?**
WILLIAM M. BENNETT, MD
From the Department of Medicine, Division of Nephrology, Hypertension, and Clinical Pharmacology, Oregon Health Sciences University, Portland.

EDITORIALS

245 **Barriers to Practice—Reality or Perception?**
KAREN M. TAIT, MD, and REBECCA J. PATCHIN, BSN, MD
From the Colusa County Health Department, Colusa, California, and the Department of Anesthesiology, Loma Linda University School of Medicine, Loma Linda University Medical Center, Loma Linda, California.

246 **Physicians and Nurse Practitioners—Old Conflicts and New Opportunities**
LEONARD J. FINOCCHIO, MPH; JANET M. COFFMAN, MPP; CATHERINE M. DOWER, JD; and EDWARD H. O'NEIL, PhD
From the Center for the Health Professions, University of California, San Francisco, School of Medicine.

248 **Parkinson's Disease—A Progress Report**
MICHAEL J. AMINOFF, MD, FRCP
From the Department of Neurology, University of California, San Francisco, School of Medicine.

(Continued on Page 184)

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WJM1096

(Continued from Page 182)

250 **A Guide of the Perplexed—Assisted Suicide**
ALBERT R. JONSEN, PhD

CORRESPONDENCE

252 **Out-of-Control Snowboarders**
SAMUEL A. WISE, MD
TERENCE M. DAVIDSON, MD, Responds

LESSONS FROM THE PRACTICE

253 **I Owe It All to Jose and His Mother**
ELIZABETH T. MATTHEWS, MD
From the Infant Evaluation Program, University Affiliated Programs, University of New Mexico School of Medicine, Albuquerque.

254 **Myopia Revisited**
SAMUEL M. CHEN, MD
From the Glendale Adventist Medical Center, Glendale, California.

OTHER FEATURES

183 **Subscription Information**

186 **Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming**

204 **Poem**

255 **In Memoriam**

256 **Instructions for Authors**

258 **Business and Subscription Information**

259 **Classified Advertising Order Form**

260 **Classified Advertising**

264 **Western State Medical Associations' Meetings**

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

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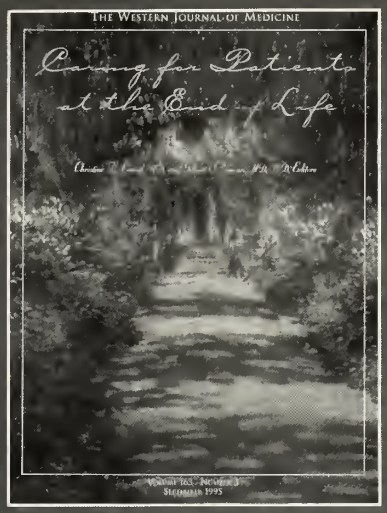

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Continuing Medical Education

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd. Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (520) 626-7832; (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

ALLERGY

December 5—**Surveillance of Vaccine-Preventable Diseases.** CDC at Distance Learning Centers. Thurs. 3.5 hrs. Contact: California Distance Learning Health Network, Claudia Kratzenstein, (619) 594-3351.

February 6-8, 1997—**Epidemiology and Prevention of Infectious Diseases: Emerging Pathogengs in the US and Worldwide.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 14.5 hrs. $415–$470. Contact: UCSF.

February 20-27, March 6-13—**Epidemiology and Prevention of Vaccine-Preventable Diseases.** Thurs. CDC at Distance Learning Centers. Thurs. 3.5 hrs. Contact: California Distance Learning Health Network, Claudia Kratzenstein, (619) 594-3351.

ANESTHESIOLOGY

January 8-11—**Anesthesiology Update 1997.** UCSD at Hotel del Coronado, Coronado, Wed-Sat. 21 hrs. $375. Contact: UCSD.

January 31-February 2—**35th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Los Angeles at Sheraton Universal Hotel, Universal City. 15 hrs. $295. Contact: David J. Stewart, MB, Prog. Dir., Pediatric Anesthesiology Conf., Children's Hospital Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

CARDIOLOGY

November 22-24—**Coronary Heart Disease Update.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sun. 11 hrs. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4569. (800) 421- 3756.

December 13-15—**14th Annual Advances in Heart Disease.** American College of Cardiology at San Francisco. Contact: ACC, (800) 253-4636, ext 695.

January 24-26, 1997—**Clinical Nuclear Cardiology: Case Review With the Experts.** American College of Cardiology at Los Angeles. Fri-Sun. Contact: ACC, (800) 253-4636, ext 695.

March 15—**Heart Disease in Women—Where Are They Now?** American College of Cardiology at Anaheim. Contact: ACC, Extramural Programs, 9111 Old Georgetown Rd., Bethesda, MD, 20897-1448

DERMATOLOGY

January 31-February 2, 1997—**Primary Care Dermatology.** UCSD at San Diego Hilton Beach and Tennis Resort. Fri-Sun. Contact: UCSD.

DRUG ADDICTION

April 17-20, 1997—**28th Annual Meeting of the American Society of Addiction Medicine.** American Society of Addiction Medicine at San Diego. Thurs-Sun. Contact: ASAM, Louisa Macpherson, Conference Coordinator, (910) 452-4920

EMERGENCY MEDICINE

December 7-8—**Stabilization and Management of the Critically Ill Child.** UCSF at Mark Hopkins Hotel, San Francisco. Sat-Sun. Contact: UCSF.

December 16-20—**Emergency Medicine Symposium II.** UCSD. Mon-Fri. 32 hrs. $495. Contact: UCSD.

February 17-21, 1997—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton Beach and Tennis Resort. 32 hrs. $495. Contact: UCSD.

March 24-15—**Emergency Medicine Symposium II.** UCSD at San Diego. Mon-Fri. 32 hrs. $495. Contact: UCSD

April 24-25—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Thurs-Fri. 16 hrs. $495. Contact: UCSD

FAMILY PRACTICE/PRIMARY CARE

December 5-6—**Controversies in Women's Health.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Fri. 13 hrs. $355. Contact: UCSF.

December 7-8—**Stabilization and Management of the Critically Ill Child.** UCSF at Mark Hopkins Hotel, San Francisco. Sat-Sun. Contact: UCSF.

January 17-19, 1997—**Practical Dermatology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Regency, La Jolla. Mon-Wed. 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego 92198. (800) 993-2632 or (619) 674-5200.

January 20-22—**Opthalmology and ENT for the Primary Care Physician.** CMEA at Hyatt Regency, La Jolla. Mon-Wed. 20 hrs. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego, 92198. (800) 993-2632 or (619) 674-5200

January 31-February 2—**Primary Care Dermatology.** UCSD at San Diego Hilton Beach and Tennis Resort. Fri-Sun. Contact: UCSD. (619) 534-3940

January 31-February 1-2—**35th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital, Los Angeles, at Sheraton Universal Hotel, Universal City. 15 hrs. $295. Contact: David J. Stewart, MB, Program Director, Pediatric Anesthesiology Conference, Children's Hospital Los Angeles, PO Box 54700, Los Angeles, CA 90054. (213) 669-2262

February 7-10—**CAFP 49th Annual Scientific Assembly.** CAFP at Hyatt Regency, San Francisco, Fri-Mon. $275-$385. Contact: Clark W. Franklin, CAFP, 114 Sansome St., Ste. 1305, San Francisco, CA 94104-3824. (415) 394-9121

February 14-16—**Office Gynecology and Women's Health for the Primary Care Physician.** CMEA at Hyatt Islandia, San Diego, Fri.-Sun. 20 hrs. $475. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego 92198. (800) 993-2632 or (619) 674-5200.

CONTINUING MEDICAL EDUCATION

February 16-21—**12th Annual Primary Care Medicine: Concepts and Controversies.** UCSF at Squaw Creek, CA 20 hrs. $625. Contact: UCSF

February 17-20—**Clinical Hematology and Oncology: 1997.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Scripps, (619) 554-8556.

February 19-23—**The Practicing Physician's Approach to the Difficult Headache Patient.** Dannemiller Memorial Educational Foundation at Marriott's Las Palmas Resort and Country Club, Rancho Mirage. Wed-Sun. 22 hrs. $345. Contact: Meeting Coordinator, Diamond Headache Clinic Research and Educational Foundation, 467 West Deming Place, Chicago, IL, 60614. (312) 388-6363

February 21—**Modern Approaches to Allergic Diseases for the Primary Care Physician.** UCSF at Moscone Center, San Francisco. Fri. 6.75 hrs. $125. Contact: UCSF

March 6-8—**Contraceptive Technology Conference.** Contemporary Forums at Fairmont Hotel, San Francisco. Thurs-Sat. 16 hrs. $425. Contact: Contemporary Forums, 11900 Silvergate Drive, Dept 265, Dublin, CA, 94568. (510) 828-7100

March 20—**Diabetes Update.** UCSF at Holiday Inn, San Francisco. 7.5 hrs. $185. Contact: UCSF

March 21-22—**Advances in Endocrinology and Metaholism.** UCSF at Holiday Inn, San Francisco. Fri-Sat. 13 hrs. $295. Contact: UCSF

March 26-28—**Annual Review in Family Medicine.** UCSF at Stanford Court Hotel, San Francisco. Wed-Fri. 16 hrs. $375. Contact: Program Coordinator, Dept. Family and Community Medicine, 500 Parnassus Ave, MU-3E, San Francisco, CA 94143-0900. (415) 476-5250

April 9-13—**Annual Scientific Program and Postgraduate Course in Fertility.** Pacific Coast Fertility Society at Rennaissance Esmeralda Resort, Indian Wells. Wed-Sun. 19 hrs. Contact: Director of Medical Education or Susan Reddy Butler, Pacific Coast Fertility Society, PO Box 1656, La Mirada, CA, 90637-1656. (310) 947-7068

April 14-15—**Born Too Soon: Multidisciplinary Strategies for Prevention of Preterm Birth.** Contemporary Forums at Marriott Hotel, Oakland. Mon-Tues. 13 hrs. $375. Contact: Contemporary Forums, 1900 Silvergate Dr., Dept. 280, Dublin, CA, 94568. (510) 828-7100, ext. 0

April 17-20—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Continuing Medical Education Associates at San Diego Hilton Beach and Tennis Resort. Thurs-Sun. 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego 92198. (800) 993-2632

INFECTIOUS DISEASE

December 5-7—**Clinical Care of the AIDS Patient.** UCSF at Sheraton Place Hotel, San Francisco.Thurs.-Sat. 24 hrs. $395. Contact: UCSF.

February 6-8, 1997—**Epidemiology and Prevention of Infectious Diseases.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

INTERNAL MEDICINE

December 8—**Endocrine Tumors: 101st Semi-Annual Cancer Seminar.** California Tumor Tissue Registry at Ritz-Carlton Hotel, San Francisco. Sun. 8 hrs. $265. Contact: CTTR, (909) 824-4788.

February 12-14, 1997—**Recent Adventures in Neurology.** UCSF at Hyatt Regency Hotel, San Francisco. Wed-Fri. 15 hrs. Contact: UCSF.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

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February 15-20—**22nd Annual Postgraduate Topics & Advances in Internal Medicine.** UCSD at Hyatt Regency, San Diego. Sat-Thurs. 52 hrs. $1365. Contact: UCSD

February 17-20—**Clinical Hematology and Oncology: 1997.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Scripps, (619) 554-8556.

March 21-27—**Internal Medicine 1997.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Fri-Thurs. 45 hrs. $795. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200

NEPHROLOGY

February 6-8, 1997—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Hotel del Coronado, San Diego. Thurs-Sat. 17 hrs. $395. Contact: UCSD

NEUROLOGY

January 17–19, 1997—**Advances in the Diagnosis and Clinical Practice in the Neurosciences.** San Diego Hilton Beach and Tennis Resort, San Diego. Fri.–Sun. 7 hrs. Contact: California Association of Neurological Surgeons, (916) 443-0236.

OCCUPATIONAL MEDICINE

December 5-6—**Occupational Disorders of the Upper Extremities.** UC Berkeley at San Francisco Airport Hilton Hotel. Thurs-Fri. Contact: UC Berkeley.

ONCOLOGY

February 17-20, 1997—**Clinical Hematology and Oncology: 1997.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Scripps, (619) 554-8556.

February 20-22, 1997—**Molecular Advances in Cancer Epidemiology and Prevention.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. Contact: UCSF

OTOLARYNGOLOGY

December 7-11—**Temporal Bone Surgical Dissection Courses.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, (213) 483-4431, ext 7079.

January 4-8, 1997—**Temporal Bone Surgical Dissection Course.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, 2100 W Third St, Los Angeles 90057. (213) 483-4431, ext 7079.

February 1-5—**Temporal Bone Surgical Dissection Course.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs. $1,300. Contact: House Ear Institute, (213) 483-4431, ext 7079.

March 15-19—**1996-1997 Temporal Bone Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat-Wed. 48 hrs. $1300. Contact: Antonio de la Cruz, MD, Director of Educaiton, House Ear Institute, 2100 W Third St, Los Angeles, CA 90057. (213) 483-4431, ext 7079.

April 12-16—**1996-1997 Temporal Bone Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat-Wed. 48 hrs. $1300. Contact: Antonio de la Cruz, MD, Director of Educaiton, House Ear Institute, 2100 W Third St, Los Angeles, CA 90057. (213) 483-4431, ext 7079.

PEDIATRICS

December 7—**Fifteenth Annual Binational Pediatric Conference.** Children's Hospital and Health Center at Mercy Hospital Education Center, San Diego. Saturday. 5 hrs. $45. Contact: Children's Hospital, Continuing Medical Education, 3020 Children's Way (5021), San Diego, 92123. (619) 576-4072.

December 7-8—**Stabilization and Management of the Critically Ill Child.** UCSF at Mark Hopkins Hotel, San Francisco. Sat.-Sun. Contact: UCSF.

January 15-18, 1997—**San Diego Cerebral Palsy Symposium.** Children's Hospital at San Diego Marriott Mission Valley. Wed-Sat. 21.5 hrs. $450-$495. Contact: Continuing Medical Education, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

January 27-31— **San Diego Conference on Responding to Child Maltreatment.** Children's Hospital at Town and Country Hotel, San Diego. Mon-Fri. 30.5 hrs. $435. Contact: Registration Coordinator, Center for Child Protection, 3020 Children's Way (MC5016), San Diego 92123. (916) 495-4940.

January 31-February 2—**35th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Los Angeles at Sheraton Universal Hotel, Universal City. 15 hrs. $295. Contact: David J. Stewart, MB, Program Dir, Pediatric Anesthesiology Conf., Children's Hospital Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

February 28-March 2—**Current Concepts in Pediatric Medicine—10th Anniversary.** Children's Hospital and Health Center at San Diego Hilton Beach and Tennis Resort. Fri-Sun. 16 hrs. $365. Contact: Children's Hospital, CME, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

April 4-5—**Pediatric Dermatology for the Practitioner.** Children's Hospital at Hyatt Islandia Mission Bay, San Diego. Fri-Sat. 12 hrs. $245. Contact: CME Office–5021, 3020 Children's Way, San Diego, CA, 92123. (619) 576-4072

PSYCHIATRY AND NEUROLOGY

February 12-14, 1997—**Recent Adventures in Neurology.** UCSF at Hyatt Regency Hotel, San Francisco. Wed.-Fri. 15 hrs. Contact: UCSF.

April 3-6—**Nelson Butler's West Coast Psychiatry Conference.** UCSD at US Grant Hotel, San Diego. Thurs-Sun. 15 hrs. $325. Contact: UCSD

RADIOLOGY

January 26-February 2, 1997—**Multi Specialty Radiology Courses: Neuroradiology, Angiographic, Interventional, Chest, Ultrasound, and Bone.** UCSD at Hotel del Coronado, San Diego. Sun-Sun. Various hours. $975. Contact: Ryals & Associates, Inc, PO Box 1925 Roswell, GA, 30077-1925. (770) 641-9773

March 29—**10th Annual Spring Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 6.25 hrs. $145. Contact: UCSD

March 30-April 4—**17th Annual San Diego Residents Radiology Review.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 41 hrs. $695. Contact: UCSD

SURGERY

January 4-8, 1997—**Temporal Bone Surgical Dissection Course.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, 2100 W Third St, Los Angeles 90057. (213) 483-4431, ext 7079.

GENERAL/MULTIDISCIPLINARY

December 12-14—**Diagnosis and Treatment of Back Pain—The Next Level.** St Mary's Hospital at Stanford Court Hotel, San Francisco. Thurs-Sat. Contact: Aubrey A. Swartz, MD, American Back Society, St Joseph's Professional Center, 2647 E 14th St, Ste 401, Oakland 94601. (510) 536-9929.

January 8, 1997—**Pre-ACLS Workshop.** AHA at San Leandro. Wed. 6 hrs. $50-$70. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro, CA 94577. (510) 632-6135

January 17, 18, 19—**ACLS Renewal/Provider.** AHA at San Leandro. Fri-Sun. 6 hrs. $100. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro, CA 94577. (510) 632-6135

February 1-2—**PALS Instructor.** AHA at San Leandro. Sat-Sun. 16 hrs. $170. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro, CA 94577. (510) 632-6135

February 8-9—**ACLS Instructor.** AHA at San Leandro. Sat-Sun. 16 hrs. $195. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro, CA 94577. (510) 632-6135

April 24-25—**New Frontiers in Alzheimer's Disease.** UCSD at San Diego Hilton. Thurs-Fri. 16 hrs. $210

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

December 6-7—**5th Update in Infectious Disease: Bugs and Drugs in the '90s.** University of Colorado Health Sciences Center at Denver. Fri-Sat. Contact: U of Colo.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

December 5-7—**American College of Physicians New Mexico Chapter Scientific Meeting.** UNM Conference Center, Albuquerque. Thu.-Sat. Contact: UNM Office of Continuing Medical Education. (505) 277-3942; FAX (505) 277-8604.

December 6-7—**Trauma Update 1996.** Holiday Inn Pyramid Hotel, Albuquerque. Fri.-Sat. Contact: UNM Office of Continuing Medical Education. (505) 277-3942; FAX (505) 277-8604.

December 11-14—**The Veterans Caucus 5th Annual Topics in the Tropics.** Sol Melia Beach and Spa Resort, Cancún, Mexico. Wed.-Sat. Contact: Sharon Hanley, RMP, Conference Coordinator, Geisinger Clinic, 100 N. Academy Ave., Danville, PA 17822-1350.

January 11-12, 1997—**15th Albuquerque Family Practice Seminar.** Albuquerque Hilton. Sat.-Sun. Contact: Ann Woodrow, Albuquerque Academy of Family Physicians, 2309 Renard SE, #208, Albuquerque, NM 87106. (505) 243-4560.

February 28-March 1—**25th Annual New Mexico Thoracic Society Lung Disease Symposium.** Taos. Fri-Sat. Contact: Billie Dytzel, 216 Truman NE, Albuquerque 87108. (505) 265-0732; (800) 221-LUNG. FAX (505) 260-1739.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

December 6-12—**Intensive MR Imaging and Neuroradiology**. Marriott Hotel, Salt Lake City. Fri-Thurs. 30 hrs. $1,250. Contact: UUSM.

February 5-9—**3rd Annual Brigham & Women's Utah Therapeutic GI Endoscopy Course 1996: Problems and Solutions.** Park City. Contact: UUSM.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UANS: Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

November 22—**Psychiatry Symposium**. Seattle. Fri. Contact: Providence/Seattle Medical Center (206) 320-2552.

November 22—**Pinkham Basic Science Lectureship**. Seattle. Fri. Contact: Swedish Medical Center (206) 386-2265.

December 3—**Tools for the Prompt Diagnosis of Colorectal and Prostate Cancer**. Seattle. Tues. Contact: Physicians' Insurance (206) 343-6526.

December 6—**17th Annual Pediatrics Conference**. Seattle. Fri. Contact: Virginia Mason (206) 223-6898.

December 12—**And the Beat Goes On: Diagnosis, Management and Malpractice in Myocardial Infarction**. Mt. Vernon. Thur. Contact: Physicians' Insurance (206) 343-6526.

December 12–14—**Annual Meeting: Washington State Chapter American College of Physicians**. Seattle. Thur.-Sat. Contact: U/W CME (206) 543-1050.

December 12–14—**The 12th Annual Infectious Disease Conference**. Seattle. Thur.-Sat. Contact: PNCEI (360) 653-4543.

December 13—**Alternative Medicine 1996**. Bellevue. Fri. Contact: Group Health Cooperative of Puget Sound (206) 326-3441.

COURSE SPONSORS AND CONTACT INFORMATION

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Articles

Surveillance of Traumatic Brain Injuries in Utah

DAVID J. THURMAN, MD, MPH, *Atlanta, Georgia*; LEW JEPPSON, MS, CINDY L. BURNETT, *and* DENISE E. BEAUDOIN, MD, MSPH, *Salt Lake City, Utah*; *and* MARGUERITE M. RHEINBERGER, JD, MPH, *and* JOSEPH E. SNIEZEK, MD, MPH, *Atlanta, Georgia*

From 1990 through 1992 we conducted surveillance of cases requiring hospital admission and of fatal cases of traumatic brain injury among residents of Utah and found an annual incidence rate of 108.8 per 100,000 population. The greatest number of injuries occurred among men and persons aged 15 to 24 years. Motor vehicles were the leading cause of injury, followed by falls and assaults. The incidence rate we found is substantially lower than previously published rates of traumatic brain injury. This may be the result of a decrease in the incidence of these injuries in the decade since earlier studies were done, as well as changing hospital admission criteria that serve to exclude less severe cases of injury. Despite the apparent decline in rates, our findings indicate the continued importance of traumatic brain injury as a public health problem and the need to develop more effective prevention strategies that will address the major causes of these injuries.

(Thurman DJ, Jeppson L, Burnett CL, Beaudoin DE, Rheinberger MM, Sniezek JE: Surveillance of traumatic brain injuries in Utah. West J Med 1996; 165:192–196)

The annual incidence rate of traumatic brain injuries in the United States has been estimated at about 200 per 100,000 population.[1,2] This estimate is founded on a small number of population-based epidemiologic studies of traumatic brain injury, most of which used data collected in limited geographic areas more than a decade ago.[3-12] To provide more reliable estimates of the incidence of traumatic brain injury in the United States today, we need more current information from more locales on the incidence of these injuries.

Recognizing this need, the National Center for Injury Prevention and Control of the Centers for Disease Control and Prevention (CDC) has developed standards for central nervous system injury surveillance and has promoted the development of traumatic brain injury surveillance programs in a number of state and local health departments. We report the current incidence of traumatic brain injury in one of these states and describe the underlying causes and the outcomes of these injuries.

Materials and Methods

We collected information on traumatic brain injuries that led to hospital admission or death among all Utah residents from January 1, 1990, through December 31, 1992. Consistent with the standards of the CDC for central nervous system injury surveillance,[13] we defined a hospitalized case of traumatic brain injury (craniocerebral trauma) as an occurrence of injury to the head resulting in admission to a hospital and associated with any of the following conditions attributed to the head injury: observed or self-reported alteration of consciousness, observed or self-reported retrograde or post-traumatic amnesia, skull fracture, objective neurologic abnormalities determined from a neurophysical examination, or diagnosed intracranial lesion(s) determined by a radiologic examination or other neurodiagnostic procedures. Fatal traumatic brain injuries were defined as deaths as a result of trauma, with head or brain injury listed on the death certificate, autopsy report, or medical examiner report in the sequence of conditions that resulted in death.

Cases were ascertained through a statewide surveillance system conducted by the Utah Department of Health's Bureau of Epidemiology. Since 1990, Utah regulations have required that all cases of traumatic brain injury be reported to the Utah Department of Health. This injury surveillance system identified cases from two sources: hospital discharge data from all acute care hospitals in the state and state vital records (death certificates). Hospital discharge data consist of compiled uniform billing and service provision records for all hospital inpatients; these records include summary diagnostic data coded according to the *International Classification of Diseases, 9th revision, Clinical Modification* (ICD-9-CM).[14] Hospitals identified traumatic brain injury cases from hospital discharge data using ICD-9-CM codes 800.0 to 801.9, 803.0 to 804.9, and 850.0 to 854.1. Cases were included if these codes appeared among any of the

From the National Center for Injury Prevention and Control, Centers for Disease Control and Prevention, Atlanta, Georgia (Dr Thurman, Ms Rheinberger, and Dr Sniezek), and the Division of Community and Family Health Services, Utah Department of Health, Salt Lake City (Mr Jeppson, Ms Burnett, and Dr Beaudoin).

This study was funded by grants from the Centers for Disease Control and Prevention: the National Center for Injury Prevention and Control and the National Center for Environmental Health, Disabilities Prevention Program.

Reprint requests to David J. Thurman, MD, MPH, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention, Mailstop F41, 4770 Buford Hwy, NE, Atlanta, GA 30341-3714.

ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control and Prevention
GCS = Glasgow Coma Score
ICD-9-CM = *International Classification of Diseases, 9th revision, Clinical Modification*

primary or secondary diagnostic fields. The department obtained hospital discharge data separately from each hospital or hospital system, not from a uniform statewide hospital discharge data set. All of the state's 40 acute care nonfederal hospitals and also its Department of Veterans Affairs medical center reported cases. In addition, department personnel reviewed individual death certificates of all cases of traumatic death in the state to determine which of these had acute traumatic brain injury listed as a contributing cause.

Hospital reports and vital records all contained personal identifiers that allowed us to match duplicate records and to construct a merged data set of all cases. Because hospital discharge data and vital records contained limited information on injury causes and outcome, we selected a 10% random sample of cases from which to obtain more information. Department personnel collected additional data for this sample by reviewing and abstracting all available corresponding medical records, state medical examiner reports, and police accident reports. When reviewers found that a report submitted by a hospital did not meet the case definition, the report was excluded from the sample and another randomly selected hospital report was substituted. For verified cases, additional information was obtained on patient demographics, cause and circumstances of injury, nature of injury, and injury severity. The records reviewers were trained and closely supervised by a physician (D.J.T. or D.E.B.) who reviewed all the abstracted data.

Cases were classified as mild, moderate, or severe using a composite of three indices of initial severity. We stratified cases based on a classification described by others[15,16] using the initial Glasgow Coma Score (GCS),[17,18] demonstrated intracranial traumatic lesions, and focal abnormalities found on neurologic examination. If no GCS was recorded, the records reviewers' classifications of the initial level of consciousness—awake, obtunded, or comatose—were used. Skull fractures were not considered intracranial traumatic lesions unless they were depressed. Mild traumatic brain injuries were those with a GCS of 13 to 15—or awake or easily awakened—without identified intracranial traumatic lesions or focal neurologic deficits. Moderate traumatic brain injuries were those with a GCS of 9 to 12—or obtunded—or those with identified intracranial lesions or focal neurologic deficits and a GCS of 9 or more. Severe traumatic brain injuries were those with a GCS of 8 or less—comatose.

Records reviewers scored injury outcome using the Glasgow Outcome Scale.[19] Outcome assessment for survivors was based only on information documented in the medical records of patients admitted to an acute care hospital.

The sample of reviewed cases was also used to evaluate the accuracy of diagnostic coding of hospital discharge data for traumatic brain injury. Predictive value-positive was defined as the proportion of persons identified by hospital discharge data as having acute traumatic brain injury who actually did meet the case definition of acute traumatic brain injury as determined by records reviewers. Predictive value-positive was calculated by a standard formula for surveillance systems.[20] We were not able to evaluate the completeness of traumatic brain injury reporting from hospital discharge data (sensitivity) because we lacked an alternative source with complete case ascertainment to use for comparison.

Confidence intervals for rates and proportions inferred from the sample were calculated according to the method described by Fleiss.[21(p14)]

Results

During the three years of this study, 5,782 cases of traumatic brain injury were reported, yielding a crude incidence rate of 108.8 per 100,000 population per year (106.3 per 100,000, age-adjusted to the 1990 US population). A preponderance of injuries occurred among men (67.7%) and among persons aged 15 to 24 years (24.8%). The median age at the time of injury was 21 years. Table 1 shows the number and rates of these injuries distributed by age and sex.

Among all reported cases there were 1,067 deaths, yielding an annual crude death rate of 20.1 per 100,000 and a case-fatality rate of 18.5%. Among these deaths, 77.3% occurred without admission to a hospital.

A random sample of 578 cases was drawn from all reported cases of traumatic brain injury. The age and sex distribution of this sample conformed closely to that of the overall group: the median age in the sample was 21 years, and most cases were male (69%). The following findings pertain to this sample group.

Initial severity is summarized in Table 2. In all, 16% of cases were considered severe at the time of hospital admission, and 13% died without hospital admission. Skull fractures were documented in 247 cases (43%). Skull fracture was the only inclusion criterion in 67 (12%) of the cases and was found in the presence of other inclusion criteria in 180 (31%) cases in this sample.

The early outcome is summarized in Table 3. For nonfatal cases, outcome was assessed at the time of discharge from acute care. Of all cases, 30% had either a fatal outcome or severe-to-moderate neurologic impairment noted at the time of the outcome assessment.

Transportation-related mishaps were the leading cause of traumatic brain injury (54.2%), followed by falls (20.6%) and nonfirearm-related assaults and firearm-related injuries (both 7.4%). Table 4 shows the distribution of injuries by cause.

The relative importance of different causes varied by age, as shown in Table 5. The rates of fall-related injury were highest in those younger than 5 years and in those

TABLE 1.—*Traumatic Brain Injuries by Age and Sex in Utah, 1990 Through 1992**

	Male		Female		Both Sexes	
Age, yr	*No.*	*Rate*	*No.*	*Rate*	*No.*	*Rate*
0 to 4	396	148.3	295	115.7	691	132.4
5 to 14	745	130.7	364	67.4	1,109	99.9
15 to 24	1,001	218.1	423	91.8	1,424	154.8
25 to 34	601	143.4	192	46.2	793	95.0
35 to 44	420	118.0	151	42.8	571	80.5
45 to 54	220	103.8	79	36.2	299	69.5
55 to 64	185	118.6	89	53.9	274	85.4
65 to 74	145	116.0	74	50.3	219	80.5
≥75	179	238.7	186	157.6	365	189.1
Unknown	22		15		37	
All ages	3,914	148.3	1,868	69.9	5,782	108.8

*Annual rate per 100,000 population.

65 years of age and older; falls were the most common cause of traumatic brain injury in these age categories. Transportation-related incidents resulted in the highest rates of injury in all other age categories.

Transportation-related injuries are further characterized in Table 6. Motor vehicles were involved in 269 of the transportation-related injuries, accounting for 47% of all 578 traumatic brain injuries in the sample. Among transportation-related injuries, 49% involved occupants of automobiles, trucks, vans, and utility vehicles. Another 15% of transportation-related injuries involved motorcycle riders, 15% involved bicyclists, and 12% involved pedestrians.

In this sample, 43 of 578 cases (7%) involved firearms, of which 35 (81%) represented suicides or suicide attempts; the remaining 8 cases involved interpersonal violence. Handguns were involved in most firearm-related injuries (25 of 43, or 58%). Most (38 of 43, or 88%) occurred in males, and a disproportionate number (16, or 37%) occurred among 15- to 24-year-olds. The ages of persons with firearm-related brain injuries ranged from 5 to 86 years; 15- to 24-year-olds were the most common age group involved. Nearly all (40, or 93%) firearm-related brain injuries were fatal; the three survivors had outcomes of either severe disability or persistent coma.

In this study, using a sample of cases, we also evaluated the quality of diagnostic data contained in hospital discharge data. During this three-year period, 555 records of presumed cases reported by hospitals were reviewed. Of these, only 494 cases met the case definition and were included in the sample of 578 described above. Thus, the predictive value-positive of case reports from hospital discharge data in this study was 89%.

TABLE 2.—*Initial Severity of Traumatic Brain Injury in Utah, 1990 Through 1992*

	Cases		
Category	*No.*	*(%)*	*(90% Confidence Interval)*
Mild	189	(32.7)	(29.5, 36.1)
Moderate	203	(35.1)	(31.8, 38.5)
Severe	90	(15.6)	(13.2, 18.3)
Died without hospital admission	76	(13.1)	(10.9, 15.7)
Inadequate description	20	(3.5)	- -
All cases	578	(100.0)	

TABLE 3.—*Outcome Severity of Traumatic Brain Injury in Utah, 1990 Through 1992*

	Cases		
Category	*No.*	*(%)*	*(90% Confidence Interval)*
Death			
Without hospital admission	76	(13.1)	(10.9, 15.7)
During hospital admission	43	(7.4)	(5.7, 9.5)
Total	119	(20.6)	(17.9, 23.6)
Persistent coma	4	(0.7)	(0.3, 1.7)
Severe disability	21	(3.6)	(2.5, 5.2)
Moderate disability	29	(5.0)	(3.6, 6.8)
Good recovery*	391	(67.6)	(64.2, 70.8)
Unknown	14	(2.4)	
All cases	578	(100.0)	

*Includes cases of patients with persisting mild neurologic deficits.

Discussion

We found an annual incidence rate of traumatic brain injuries in Utah that is much lower than incidence rates described in previous studies.[3-12] There are several possi-

TABLE 4.—*Distribution of Traumatic Brain Injuries by Cause in Utah, 1990 Through 1992*

	Cases		
Category	*No.*	*(%)*	*(90% Confidence Interval)*
Vehicles and transport	313	(54.2)	(50.7, 57.7)
Falls	119	(20.6)	(17.9, 23.6)
Assault, nonfirearm	43	(7.4)	(5.7, 9.5)
Firearms	43	(7.4)	(5.7, 9.5)
Sports and recreation	35	(6.1)	(4.6, 8.0)
Other	20	(3.5)	(2.4, 5.1)
Unknown	5	(0.9)	
All causes	578	(100.0)	

TABLE 5.—*Traumatic Brain Injury by Age and Cause in Utah, 1990 Through 1992**

	Transport		Nonfireorm Assoult		Fireorms		Falls		Sports or Recreotion	
Age, yr	Rote	90% CI	Rote	90% CI	Rote	90% CI	Rote	90% CI	Rote	90% CI
0 to 4	30.7	19.7, 46.9	23.0	13.7, 37.7	0.0	- -	70.9	53.7, 92.9	1.9	0.1, 10.1
5 to 14	55.9	45.5, 68.4	1.8	0.4, 6.1	0.9	0.1, 4.7	16.2	10.7, 24.2	7.2	3.7, 13.3
15 to 24	117.4	101.1, 135.7	10.9	6.1, 18.7	18.5	12.0, 27.9	5.4	2.3, 11.8	16.3	10.3, 25.3
25 to 34	61.1	48.4, 76.6	7.2	3.3, 14.6	8.4	4.1, 16.1	10.8	5.8, 19.2	8.4	4.1, 16.1
35 to 44	46.6	34.6, 62.1	14.1	7.9, 24.3	9.9	4.9, 19.0	12.7	6.9, 22.6	4.2	1.3, 11.5
45 to 54	25.6	14.8, 42.9	4.7	1.0, 15.7	2.3	0.2, 12.2	16.3	8.0, 31.3	0.0	- -
55 to 64	46.7	29.5, 72.5	0.0	- -	12.5	4.7, 29.7	34.3	19.9, 57.5	3.1	0.2, 16.4
≥65	36.6	23.8, 55.2	2.2	0.1, 11.3	12.9	6.0, 26.2	49.5	34.4, 70.2	0.0	- -

CI = confidence interval

*Annual rate per 100,000 population.

TABLE 6.—*Types of Transportation-Related Traumatic Brain Injuries in Utah, 1990 Through 1992*

	Coses		
Category	No.	(%)	(90% Confidence Intervol)
Automobile	99	(31.6)	(27.3, 36.2)
Small truck or utility vehicle	47	(15.0)	(11.8, 18.8)
Motorcycle	46	(14.7)	(11.6, 18.5)
Pedestrian	37	(11.8)	(9.0, 15.3)
Bicycle–motor vehicle collision	20	(6.4)	(4.3, 9.3)
Bicycle	27	(8.6)	(6.2, 11.8)
All-terrain vehicle	10	(3.2)	(1.8, 5.5)
Equestrian	15	(4.8)	(3.0, 7.4)
Other*	12	(3.8)	(2.3, 6.2)
All transportation-related causes	313	(99.9)	

*Includes injuries due to falls from moving vehicle (5), large truck collision (3), other motor vehicle collision (2), and non–motor-vehicle incident (2).

ble explanations. Between 1979 and 1992, the national mortality of traumatic brain injury has declined 22%.[22] A similar decline in the morbidity of traumatic brain injury appears likely during this period. The decline of nearly 50% in combined mortality and morbidity found in our study appears disproportionately large, however, and requires further explanation. It is possible that traumatic brain injury rates in Utah are lower than in other areas of the United States, although the rate of all types of fatal injuries in Utah is only 4% lower than the corresponding US rate.[23] A major part of the reduction in the number of reported cases of brain injury may be due to changes in hospital admission criteria that result in fewer admissions of persons with mild injuries. This assumption is supported by comparing case-fatality ratios and proportions of moderate and severe brain injury found in our study with those of previously published studies, which shows that the indices of severity in our samplé are considerably higher than in most of the previous studies.[2]

These numbers show that traumatic brain injury remains a major public health problem and requires new and more effective prevention strategies. These findings indicate the continued need to focus prevention programs on specific causes and risk groups: motor vehicles, which commonly cause injuries in all ages but occur with the greatest frequency among men in late adolescence and young adulthood; falls, which are most frequent among the youngest and oldest age groups; and assaults and other intentional injuries, including those involving firearms, which are most common among adolescent and young adult men.

Finally, this study shows that the diagnostic data on traumatic brain injury obtained from hospital discharge data sets are reasonably accurate, as shown by the predictive value-positive of 89%. Although we cannot quantify the sensitivity of this surveillance system, the methods used and consistency of data among reporting sources suggest a high sensitivity. We conclude that the quality of diagnostic hospital discharge data is adequate for the purposes of surveillance.

Conclusion

This study illustrates the usefulness of a state-based surveillance system of traumatic brain injury using recently developed CDC standards. Comparable injury surveillance in many US locales is needed to describe the national incidence, risk factors, causes, and severity. This surveillance will promote the development of more effective prevention programs, and by monitoring incidence trends over time, we will be able to assess the effectiveness of these programs.

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Articles

Sputum Gram's Stain in Community-Acquired Pneumococcal Pneumonia

A Meta-analysis

LTC WILLIAM W. REED, MPH, MC, USA; GREGORY S. BYRD, MD; *and*
COL ROBERT H. GATES Jr, MC, USA, *Aurora, Colorado*; ROBIN S. HOWARD, MA, *Washington, DC*; *and*
MICHAEL J. WEAVER, MD, *Aurora, Colorado*

The usefulness of the sputum Gram's stain is controversial. This meta-analysis was designed to evaluate the sensitivity and specificity of the sputum Gram's stain in community-acquired pneumococcal pneumonia. Using a predetermined protocol, articles were discovered through a MEDLINE search (1966 to 1993) and the examination of bibliographies and were graded for quality by three blinded reviewers. Information on the reference standard, blinding, stain interpreter, control for antibiotic use, and definition of a positive test was collected. We found 12 articles containing 17 test characteristics to evaluate. The number of patients in each study ranged from 16 to 404. Sputum culture was the most common reference standard (10 of 17 estimations). Sensitivity ranged from 15% to 100% and specificity from 11% to 100%. Test characteristics varied markedly among studies and appeared related partly to the test interpreter. The sputum Gram's stain may yield misleading results in community-acquired pneumonia, as its sensitivity and specificity vary substantially in different settings. A practitioner electing to use the study should be well trained and use a specific definition for a positive test.

(Reed WW, Byrd GS, Gates RH Jr, Howard RS, Weaver MJ: Sputum Gram's stain in community-acquired pneumococcal pneumonia—A meta-analysis. West J Med 1996; 165:197–204)

Pneumonia is the sixth leading cause of death in the United States, accounting for more than 500,000 hospital admissions per year.[1] The case-fatality rate for pneumococcal pneumonia among patients admitted to a hospital was 9% in a recent prospective study[2] and ranges from 4% to 27% in published articles.[2–9]

The sputum Gram's stain is an inexpensive, rapidly performed test that is widely advocated as useful in identifying the etiologic agent in community-acquired pneumonia,[10–12] although the test has been criticized as unreliable.[13] We conducted a meta-analysis of published English-language articles to evaluate the sensitivity and specificity of the sputum Gram's stain in community-acquired pneumococcal pneumonia. We also wanted to determine whether a variation in test characteristics was related to factors such as the stain interpreter, the definition of a positive Gram's stain, or control for antibiotic use before testing.

Methods

Evaluation of Studies

Following a written protocol, we used the MEDLINE computer service to generate a list of relevant articles, using the key words "sputum," "Gram's stain," and "pneumonia." The bibliographies of these articles were searched to discover other pertinent articles. Of a total of 180 articles that were found, 27 compared the sputum Gram's stain with an independent reference standard and were assessed by reviewers (G.S.B., M.J.W., and R.H.G.) blinded to author and journal.[4,9,14–38] Reviewers judged whether articles met criteria for inclusion in the meta-analysis, specifically whether patients had community-acquired pneumonia, whether sputum Gram's stains were compared with an independent reference standard, and whether sufficient information was available to generate a 2×2 table of true-positives, true-negatives, false-positives, and false-negatives. Reviewers also assessed the quality of each study by determining whether inclusion and exclusion criteria were explicit; whether intraobserver and interobserver variability was assessed; the training of the test interpreter; whether the assessment of Gram's stain test characteristics was a specific objective of the study; and the general clarity of the study. In judging quality characteristics, reviewers used their own criteria for scoring.

From the Department of Medicine, Fitzsimons Army Medical Center, Aurora, Colorado (Drs Reed, Byrd, Gates, and Weaver), and the Department of Clinical Investigation, Walter Reed Army Medical Center, Washington, DC (Ms Howard).

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense. All authors were US government employees while the work was being done on this project. The article therefore fits the description in the US Copyright Act of 1976 of a "US government work" and cannot be copyrighted.

Reprint requests to LTC William W. Reed, MD, MPH, MC, USA, Dept of Medicine, Tripler Army Medical Center, Honolulu, HI 96859-5000.

Seven articles initially reviewed met criteria for inclusion in the meta-analysis.[17,21,24–26,29,36] We wrote letters to the authors of all 27 articles, requesting raw data and clarification of other issues specified in our protocol, such as whether Gram's stain interpreters were blind to the reference standard results or vice versa and whether sputum was obtained before antibiotic use when such information was not explicitly given in the article. From this correspondence, we gained enough data to calculate sensitivity and specificity for five additional articles,[9,18,27,28,31] giving a total of 12 articles used in our analysis.

Statistics

A summary receiver-operator characteristic (ROC) curve was estimated using the methods proposed by Moses and colleagues.[39] This approach permits the combining of several independent studies of the same diagnostic test, where each study reports an estimated false-positive rate (equal to 1-specificity) and an estimated true-positive rate (sensitivity). The false-positive and true-positive rates are converted to logistic transformations, thereby defining a set of points. A regression line is fitted to the set of points so defined. Finally, the line is back-transformed to the relevant region of the ROC space.

Several studies provided results using different standards[21,26] or interpreters[28] for the same sample of subjects. To avoid overrepresenting one sample of patients when estimating the summary ROC, we used weighted linear regression, with each sample of patients represented equally. The "relevant range" summary ROC curve was calculated by excluding those studies with sensitivity or specificity below 50%. To explore the influence of study blinding, antibiotic use, Gram's stain definition, stain

TABLE 1.—*Characteristics of Studies of Sputum Gram's Stain Included in Analysis*

*Reference**	*Patients, No.*	*Purulent Sputum, %†*	*Reference Standard*	*Control for Antibiotics?‡*	*Blinded?§*	*Definition‖*	*Interpreter¶*	*Sensitivity, %*	*Specificity, %*
British Thoracic Society, 1987[9]	404	NA	Combination	No	No	>50% organisms	Lab tech	15	98
Dans et al, 1984[17]	154	NA	Sputum	No	Yes	Unknown	House officer or student	52	88
.....	147	NA	Sputum	No	Yes	Unknown	House officer or student	63	80
Kalin et al, 1983[18]	71	76	Sputum	Yes	No	>10/oif	ID	84	85
Thorsteinsson et al, 1975[21]	16	NA	Sputum	Yes	No	Unknown	Unknown	100	67
.....	16	NA	Transtracheal	Yes	No	Unknown	Unknown	100	67
.....	15	NA	Bronchial	Yes	No	Unknown	Unknown	100	67
Boerner and Zwadyk, 1982[24]	76	92	Sputum	No	Yes	>50% organisms	House officer	94	64
Gleckman et al, 1988[25]	59	NA	Blood	Yes	Yes	>10/oif	Lab tech	69	83
Rein et al, 1978[26]	28	NA	Sputum	Yes	Yes	>50% organisms or >10/oif	Fellow	60	61
.....	42	NA	Combination	Yes	Yes	>50% organisms or >10/oif	Fellow	62	85
Lentino and Lucks, 1987[27]	40	NA	Sputum	No	Yes	>50% organisms	Fellow	55	94
Merrill et al, 1973[28]	53	NA	Sputum	Yes	Yes	Unknown	House officer or student	96	11
.....	30	NA	Sputum	Yes	Yes	Unknown	Lab tech	43	88
Xiaoping et al, 1988[29]	95	90	Sputum	No	Yes	>10/oif	Pulmonary	88	85
Lim et al, 1989[31]	40	NA	Combination	Yes	Yes	>50% organisms or >10/oif	Fellow	67	100
Fine et al, 1991[36]	36	47	Combination	No	Yes	>50% organisms	House officer	86	72

NA = not available

*Dans et al[17] included data for 2 distinct studies conducted in different years. Thorsteinsson et al,[21] Rein et al,[26] and Merrill et al[28] used the same patient population for different studies.
†Percentage of patients producing purulent sputum.
‡Yes indicates no antibiotic use before a sputum specimen was collected.
§Yes indicates that stain interpreter was blind to reference standard results.
‖Definition: >10/oif indicates an average of >10 organisms of proper pneumococcal structure per oil-immersion field; >50% organisms indicates that >50% of organisms on slide are of proper pneumococcal structure.
¶Lab tech refers to laboratory technician, student refers to medical student, Fellow indicates infectious disease fellow or attending physician, and Pulmonary refers to pulmonary staff.

TABLE 2.—*Quality Characteristics of Studies in Analysis as Judged by Blinded Reviewers*

*Reference**	*Inclusion/Exclusion Criteria**	*Clarity of Definition†*	*Intra/Interobserver Variability‡*	*Interpreter Training§*	*Objective‖*	*Overall Clarity*
British Thoracic Society, 1987[9]	Fair	Unclear	No	Unclear	Secondary	Fair
Dans et al, 1984[17]	Fair	Unclear	No	Fairly clear	Secondary	Fair
Kalin et al, 1983[18]	Good	Clear	No	Unclear	No	Fair
Thorsteinsson et al, 1975[21]	Fair	Unclear	No	Unclear	Secondary	Fair
Boerner and Zwadyk, 1982[24]	Fair	Fairly clear	No	Clear	Primary	Fair
Gleckman et al, 1988[25]	Fair	Clear	No	Fair	Secondary	Fair
Rein et al, 19782[6]	Fair	Clear	No	Clear	Primary	Good
Lentino and Lucks, 1987[27]	Fair	Clear	No	Unclear	Primary	Fair
Merrill et al, 1973[28]	Fair	Unclear	No	Fair	Secondary	Fair
Xiaoping et al, 1988[29]	Fair	Clear	No	Unclear	Secondary	Fair
Lim et al, 1989[31]	Good	Fairly clear	No	Unclear	No	Fair
Fine et al, 1991[36]	Good	Clear	No	Clear	Primary	Good

*Refers to the clarity of the inclusion and exclusion criteria.
†Refers to the clarity of the definition of a positive sputum Gram's stain result.
‡Refers to the assessment of interobserver and intraobserver variability.
§Refers to the clarity of the description of the training of interpreters of sputum Gram's stain.
‖Assesses whether test characteristics of sputum Gram's stain were primary or secondary objective of the study or not an objective.

interpreter (ranked according to level of training), and study size, we included these variables in the summary ROC model.[39,40] All *P* values are two-sided.

Results

Characteristics of the accepted studies are given in Table 1. Only 4 of 12 articles contained information on the ability of patients to produce purulent sputum, which ranged from 47% to 92%, or 70% overall (399 of 569 patients). All but 4 studies (references 9, 17, 21, and 28) explicitly said that only purulent sputum was used for Gram's staining. Reference standards included sputum culture, culture of transtracheal aspirate, culture of bronchial aspirate, or a combination reference standard in which the result was deemed positive if one or more of several tests were positive. Blood culture was not evaluated as a reference standard because of poor sensitivity, except in one study in which all patients had bacteremia.

Study quality as defined by specific criteria is displayed in Table 2. Determining the performance characteristics was a primary objective in only 4 of the 12 studies. The definition used for a positive Gram's stain was judged to be clear in only 6 of the studies. In none of the studies was there any assessment of intraobserver or interobserver variability regarding the interpretation of Gram's stains.

Three basic definitions were used for a positive Gram's stain: an average of greater than 10 organisms of proper pneumococcal structure per oil-immersion field, greater than 50% of organisms on the slide of proper structure, or when either of these two criteria were met. For 12 of 17 estimations, the interpreters of the Gram's stain were judged blinded to the results of the reference standard. Smears were prepared mostly by technicians and house officers. Interpretation was done by attending physicians or fellows on the infectious disease or pulmonary service, laboratory technicians, house officers, or medical students.

Sensitivity ranged from 15% to 100% and specificity from 11% to 100%. In 7 of the 12 studies, the sputum Gram's stain had a sensitivity of less than 70%, meaning that nearly a third of patients with evidence of pneumococcal pneumonia had a false-negative Gram's stain. Of note, even those studies where an expert—the infectious disease or pulmonary specialist—interpreted the stain, only two of five studies had a sensitivity of 70% or greater. Finally, none of the three studies where the smear was reviewed by a laboratory technician (a likely interpreter in many hospital settings) had a sensitivity greater than 70%. Indeed, the sensitivity in these last three studies was poor: 15%, 43%, and 69%.

Of the four studies that used combination reference standards, three included blood, sputum, and pleural fluid cultures as part of the reference standard,[9,31,36] and two also included pneumococcal antigen in serum, urine, or sputum.[9,31] One used a combination of sputum culture, quellung reaction, and mouse inoculation for its reference standard.[26]

Figure 1 depicts the test characteristics of all studies; a summary ROC curve is shown. In Figure 2, studies are identified by the reference standard. In Figure 3, studies are identified according to the definition of a positive Gram's stain. Studies are classified according to test interpreter in Figure 4. Study size, study blinding, the definition of a positive test, and control for antibiotic use were not statistically related to test characteristics. This result must be interpreted with caution in light of the small number of studies evaluated. There was a trend ($P = .07$) for interpreter level of training to be positively associated with diagnostic accuracy. The only two studies with both sensitivity and specificity greater than 80% used infectious disease or pulmonary specialists as interpreters and a definition of greater than 10 organisms per oil-immersion field.

Discussion

Our results cast considerable doubt on the usefulness of the sputum Gram's stain in community-acquired

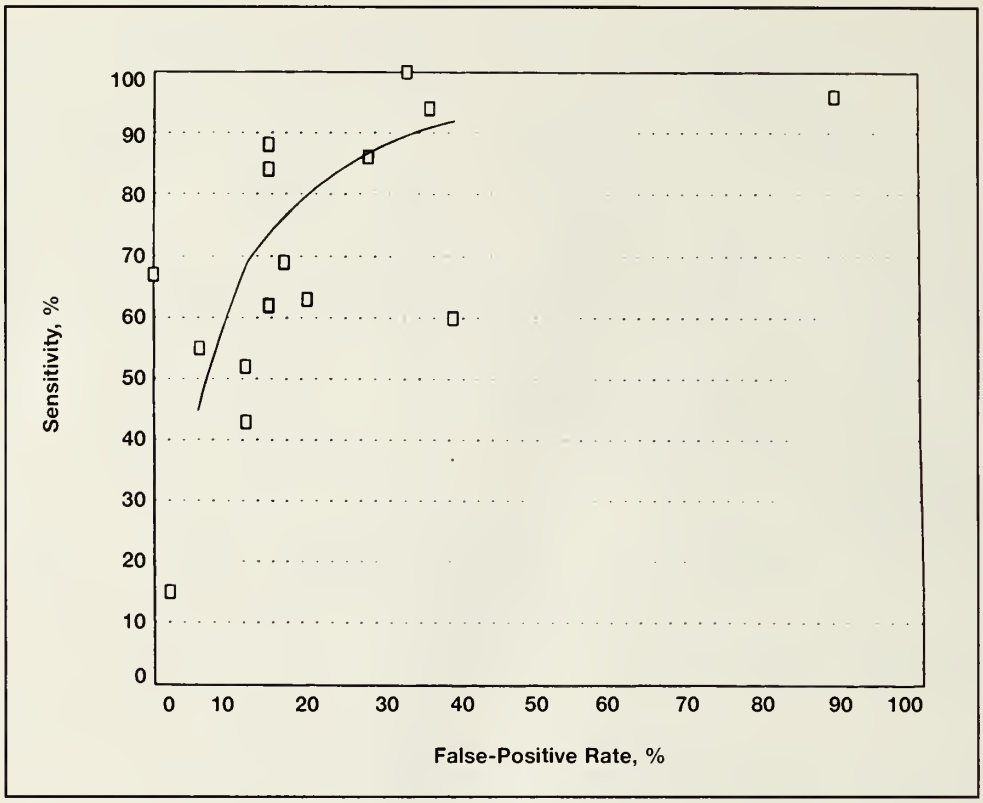

Figure 1.—Test characteristics of all studies with summary receiver-operator characteristic curve are shown.

pneumococcal pneumonia. Nearly a third of the patients were unable to produce adequate sputum—although only four studies reported this information—and there is pronounced variation among the studies in estimated sensitivity and specificity of the sputum Gram's stain. Some variation results from using different thresholds for a positive test. As the definition of a positive test becomes more lenient, sensitivity increases and specificity declines.[41] Not all of the variation in our analysis can be explained by this phenomenon, however, or all points would lie on the summary ROC curve.

Regardless of its source, the variation in sensitivity and specificity noted is likely to be confusing and even hazardous in a clinical setting. To understand the implications of a particular test result, each stain interpreter must determine the sensitivity and specificity for his or her technique of interpretation. Failure to do so could lead, for instance, to serious undertreatment. For example, if an interpreter assumed without confirmation that her Gram's stain interpretation was highly specific for pneumococcal pneumonia, she might treat with penicillin alone, despite the relatively high false-positive rate in many studies. Indeed, among house officers and students, the false-positive rate (equal to 1-specificity) was greater than 20% in four of five studies. It is important to note that our data come from research studies in which the participants generally knew they were being observed. In the setting of a rural emergency department or small urban community clinic, the Gram's stain might have even lower sensitivity and specificity.

The idea that the sputum Gram's stain is simple and inexpensive has probably been overstated. The initial step of obtaining a sputum specimen is often not successful and may lead to wasted efforts by nurses and respiratory therapists. Our data suggest that the level of training may be important for interpreting Gram's staining; thus, the time and expense of expert training is a part of the cost of the test as well. It is important to consider that the average community practitioner in the United States spends an average of 16 minutes per office visit, with 70% of visits lasting 15 minutes or less.[42] The time necessary to do a careful interpretation is not trivial under these conditions. One approach for a clinician under such circumstances might be to request interpretation by a laboratory technician. In the three studies in which the smear was reviewed by a laboratory technician, however, sensitivity was less than 70%.

We have chosen the term "reference standard" rather than "gold standard" because there is no universally accepted gold standard for the sputum Gram's stain. A sputum culture was the most commonly used reference standard in our analysis and has been criticized for lack of both sensitivity and specificity.[13,22,43,44] Blood culture is a reference standard that is highly specific but poorly sensitive compared with an ideal gold standard. In some published studies, sputum cultures were likely to be positive in patients with pneumonia and pneumococcal bacteremia,[3,20,25] whereas other studies have shown a poorer correlation.[18,35,45]

Although the lack of an ideal gold standard for identi-

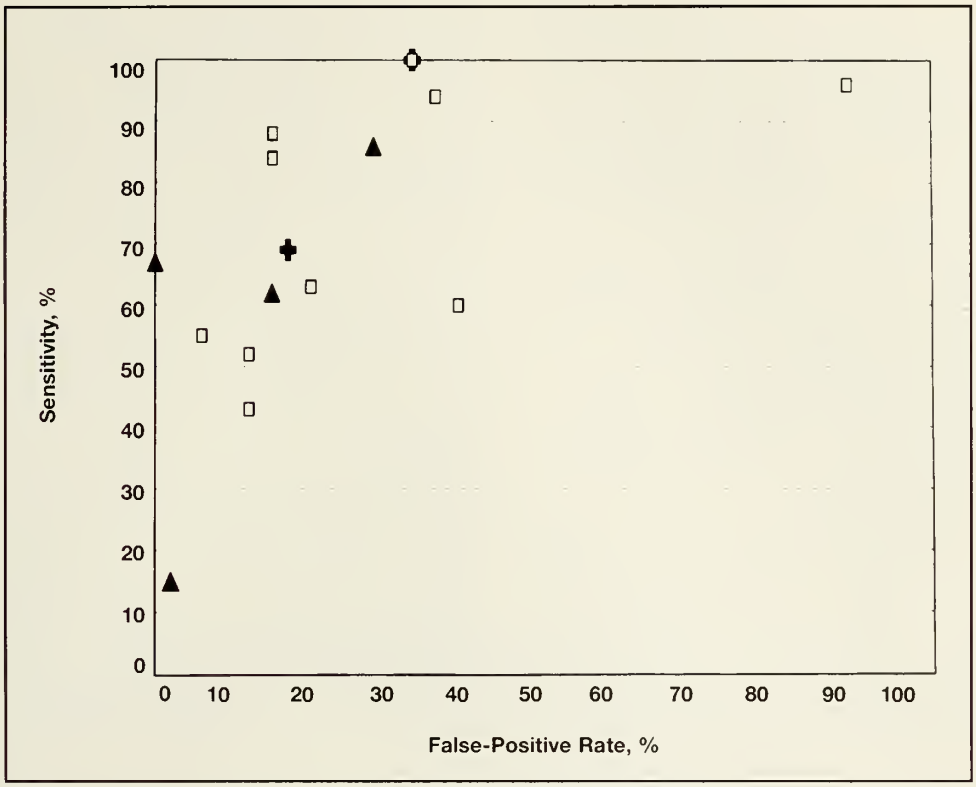

Figure 2.—Test characteristics are shown of studies identified by the reference standard. □ = sputum culture, ▲ = combination of tests (see Table 1), ✚ = other (blood culture, transtracheal aspirate culture, bronchial aspirate culture).

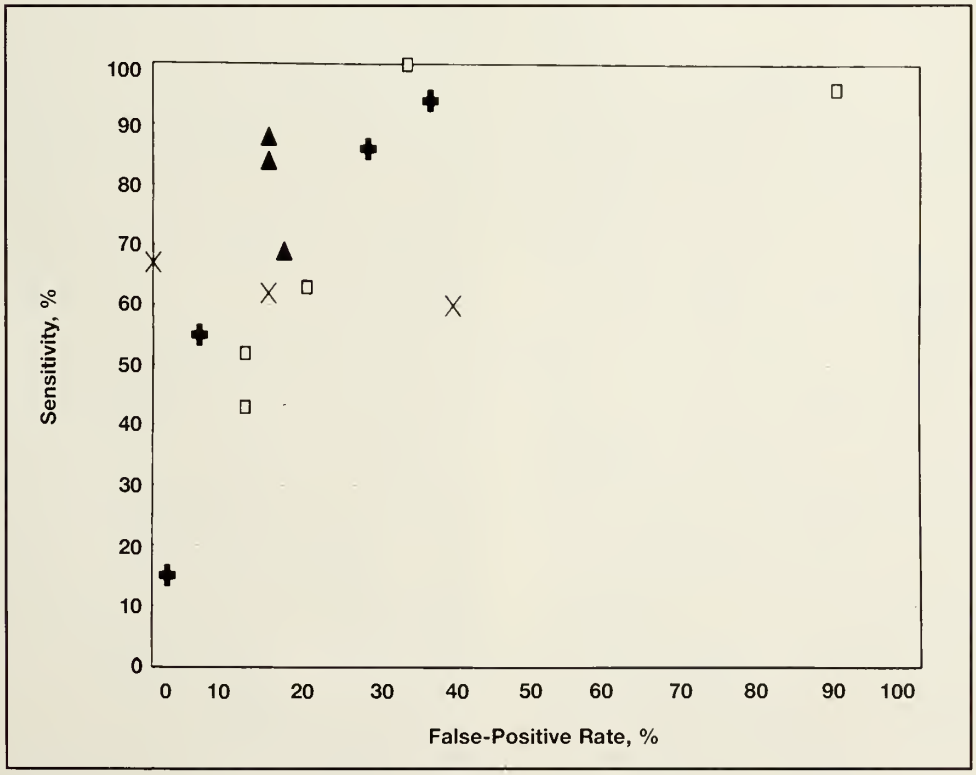

Figure 3.—Test characteristics are shown of studies identified by the definition of a positive Gram's stain. ▲ = >10 organisms/oil-immersion field, ✚ = >50% of organisms/oil-immersion field, × = >10/oil-immersion field or >50% (see Table 1), □ = unknown.

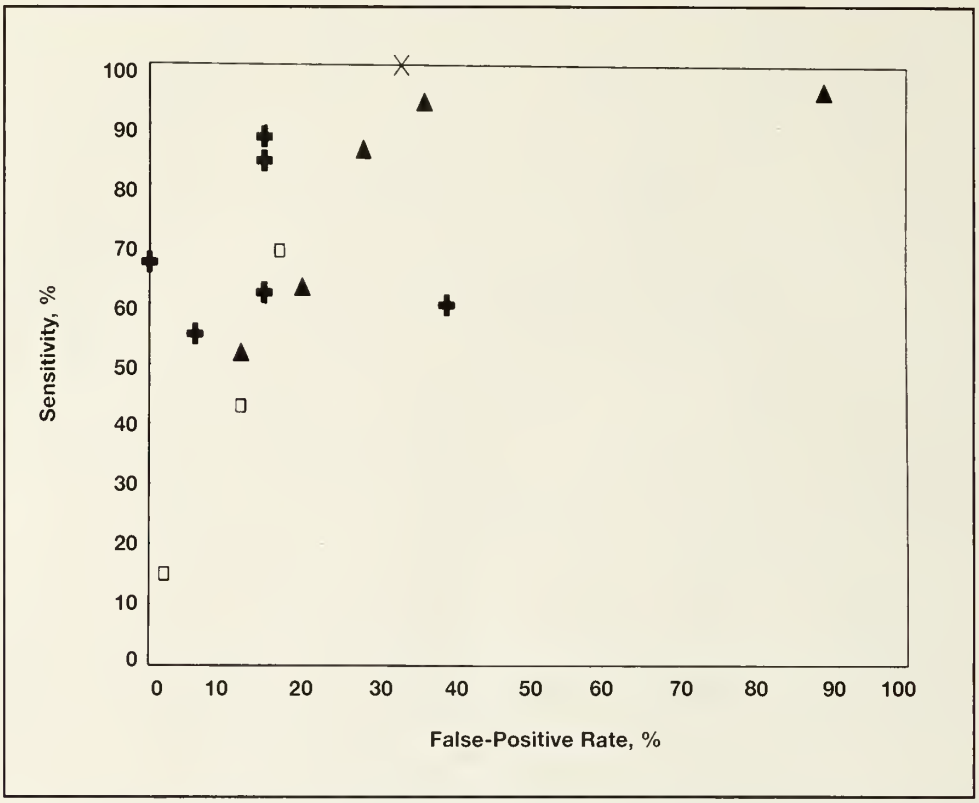

Figure 4.—Test characteristics are shown of studies identified by the interpreter of the Gram's stain. ✚ = infectious disease or pulmonary service staff or fellow, ▲ = house officer or medical student, □ = laboratory technician, × = unknown.

fying the etiologic agent in pneumonia complicates the interpretation of our results, it should be noted that the Gram's stain fared no better in the seven estimations that used reference standards other than a sputum culture. Some studies in our analysis used a combination reference standard.[9,26,30,31] For these studies, we have considered a positive result to exist when any of the components of the combination standard are positive. This approach should produce high sensitivity and low specificity, but this prediction is not borne out by our analysis. Two of these studies used the pneumococcal antigen test.[9,31] When an imperfect reference standard is used, the perceived sensitivity and specificity of the diagnostic test may be either better or worse than the actual test characteristics, depending on whether the test and the reference standard both misclassify the same patients.[46] There are not sufficient data on this issue to determine whether the test characteristics in the studies we analyzed would have been better or worse when compared with an ideal gold standard.

The studies analyzed in this review differed considerably in specific quality criteria, as shown in Tables 1 and 2. Whereas some studies had the estimation of the test characteristics of the sputum Gram's stain as a primary objective, other studies were primarily concerned with evaluating the cause of pneumonia or with the characteristics of a different test, such as the quellung reaction or pneumococcal antigen. All studies were prospective except for one that was a retrospective chart review.[17] By contacting the authors of these studies, we were able to evaluate raw data and to clarify specific questions related to our protocol. In some instances, this allowed us to include studies that would have been otherwise excluded. Because we had specific criteria for including studies and because our questions for the authors came from an a priori protocol, we think that our approach reduced publication bias and led to more accurate assessments of the characteristics of the studies analyzed. We did not search for unpublished studies, which is a possible source of bias in our analysis, but the results of such studies would be unlikely to alter our finding of pronounced variation of test characteristics for the sputum Gram's stain in different settings.

Guidelines for the conduct of a meta-analysis evaluating a diagnostic test have been published and were used in the design of our analysis.[40] This form of meta-analysis emphasizes the use of graphic displays to help explain the variability in study results. Unlike a meta-analysis of clinical therapeutic trials, a single summary statistic of results is often not appropriate in this type of meta-analysis. Instead, the summary ROC curve is used to describe how sensitivity and specificity would vary in relation to one another as a result of combining independent studies.

We recommend that practitioners who elect to use this test to guide therapy be taught a specific definition for a positive Gram's stain: an average of greater than 10

organisms of the proper pneumococcal structure per oil-immersion microscopic field in purulent sputum may be a reasonable choice. Competence not only at recognizing specific bacterial types but at adhering to a specific definition should be tested. For an individual patient, the pretest likelihood of pneumococcal pneumonia being present should be estimated whenever possible to aid interpretation of the Gram's stain result. Grading tests as weakly or strongly positive may also improve diagnostic accuracy—for example, defining greater than 20 organisms per oil-immersion field for a strongly positive test. Although its limitations in community-acquired pneumococcal pneumonia have been discussed, we have not assessed other special situations in which the sputum Gram's stain may prove to be helpful. The studies reviewed do not allow an assessment of the likelihood of "atypical" pneumonia or noninfectious lung disease in the presence of a properly done and reviewed Gram's stain that fails to reveal bacteria. Also not addressed is the use of the Gram's stain to detect organisms such as *Nocardia* species; *Haemophilus influenzae*, which may mimic *Pneumocystis carinii* in human immunodeficiency virus disease; and *Staphylococcus aureus* in nonresponding pneumonitis. The finding of these organisms may specifically alter therapy.

Conclusion

No single estimation of sensitivity and specificity can be made regarding the sputum Gram's stain in community-acquired pneumococcal pneumonia. Test characteristics vary dramatically depending on several factors. Thus, the sputum Gram's stain may be misleading, and its use may even be hazardous, especially if its interpreter is not well trained according to specific guidelines. Further studies may help clarify the role of the sputum Gram's stain in community-acquired pneumonia.

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* * *

Transubstantiation

Morning and a gray day wrapped
in rain and fog and Punxatawney Phil
saw six more weeks of winter.

Mr. Kelly has tapped out at eighty-three.

I started sad then hummed a bar
and shuffle-stepped across the floor
splashing puddles in my head.
My white socks spun just like Gene
who made it seem so easy
that even I could dance.

He played his ode to joy in Technicolor
radiant as stained glass. Gene Kelly's smile
beneath a downpour transmuted dance and song
and made a blessing out of rain.

CATHERINE CLARK-SAYLES
Mill Valley, California

Articles

When Patients Ask About Assisted Suicide
A Viewpoint From Oregon

MELINDA A. LEE, MD; LINDA GANZINI, MD; *and* KENNETH BRUMMEL-SMITH, MD, *Portland, Oregon*

The passage of the Oregon Death With Dignity Act has profound implications for the prevailing model of care for dying patients. Patients are already asking for assisted suicide. Most physicians have not been trained in evaluating these requests in a therapeutic way. We discuss the issues around the needs of dying patients and, regardless of the legal status, what to do when patients ask for a lethal dose of medication. With the tools to explore the meaning of these requests, physicians will be better able to understand and meet the needs of their dying patients.

(Lee MA, Ganzini L, Brummel-Smith K: When patients ask about assisted suicide—A viewpoint from Oregon. West J Med 1996; 165:205–208)

On November 8, 1994, the Oregon electorate approved the Oregon Death With Dignity Act, making it legal for a physician to write a prescription for a lethal dose of medication for a terminally ill patient who requests it.[1] This measure narrowly passed by a margin of 51% of voters in favor to 49% opposed. The law was scheduled to take effect 30 days after the election, but has been blocked by a series of injunctions since two physicians and several terminally ill patients sought to prevent its implementation by filing a lawsuit.[2] On August 3, 1995, a federal district judge found the act unconstitutional, arguing that it failed to offer equal protection against suicide to terminally ill persons. This decision is currently under review by the Ninth United States Circuit Court of Appeals, the same court that found the Washington State law banning assisted suicide in violation of liberty interests guaranteed by the 14th Amendment. In a related decision, the Second US Circuit Court of Appeals recently ruled that a New York law prohibiting assisted suicide is unconstitutional. The US Supreme Court has agreed to review these lower court decisions in the next few months.

National attention is focused on these legal tests as Americans continue to debate whether physician-assisted suicide will become an accepted practice. Regardless of whether or not assisted suicide is legalized, growing public acceptance, the heightened debate, and increased media attention to the issue have resulted in new demands on physicians. It has been well documented that patients are already asking for assisted suicide.[3-5] A survey of Oregon physicians months after the 1994 election found that 21% had been asked for a lethal prescription by a terminally ill patient in the preceding year.[3] At present, physicians lack models for discussing and evaluating in a therapeutic way patients' requests for assisted suicide. In this article, we reflect on the elements of a therapeutic initial response to a request for assisted suicide. Regardless of the outcome of the pending legal appeals, having the tools to explore the meaning of a request for assisted suicide will enable physicians to better understand and meet the needs of dying patients.*

The Oregon Initiative

If enacted, the Oregon law will allow a physician to prescribe a lethal dose of medication to an adult who requests it if the patient is competent, informed, and expected to die within six months. The prescription is to be self-administered by the patient. The right of the physician to decline to participate for moral or professional reasons is a clear prerogative. Other procedural safeguards are built into the statute. For example, to be eligible, a patient must be an Oregon resident, although the law does not define "resident." Only a physician who has primary responsibility for the patient and for treatment of the terminal disease is qualified to write a lethal prescription. The prognosis must be confirmed by a second physician. The patient must make two oral requests, separated by 15 days, and one written request. If the primary physician suspects that the patient may have a mental disorder that could affect judgment, the physician must refer the patient for counseling by a psychiatrist or a psychologist before writing the prescription. The law also requires the physician to request that the patient disclose his or her intentions to the family, but the patient may refuse. Insurance companies may not

*See also the editorial by A. R. Jonsen, PhD, "A Guide of the Perplexed—Assisted Suicide," on pages 250–251 of this issue.

From the Departments of Medicine (Drs Lee and Brummel-Smith), Psychiatry (Dr Ganzini), and Family Medicine (Dr Brummel-Smith), Oregon Health Sciences University; the Gerontology Section (Dr Lee) and Geriatric Psychiatry (Dr Ganzini), the Medical and Psychiatry Services, Veterans Affairs (VA) Medical Center; and the Division of Long-Term Care, Providence Health Systems (Dr Brummel-Smith), Portland.

The conclusions and opinions in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs or Providence Health Systems.

Reprint requests to Melinda Lee, MD, Medical Service (111-P), VA Medical Center, PO Box 1034, Portland, OR 97207.

ABBREVIATIONS USED IN TEXT

AMA = American Medical Association
OMA = Oregon Medical Association

withhold death benefits from the survivors of a patient who acts in accordance with the law. The law also prohibits the disciplining of physicians and other health care professionals who participate. Documentation that requirements have been met must be confidentially reported to the Oregon Health Division. Health care professionals who act in good faith according to this law are exempt from criminal and civil liability.

Legalization—A Mixed Message for Providers

The American Medical Association (AMA), the American Nurses' Association, and the American Geriatrics Society have all issued position statements opposing health care providers' participation in assisted suicide.[6–8] Because its membership was almost evenly split on the issue, the Oregon Medical Association (OMA) officially decided not to support or oppose the Oregon Death With Dignity Act during the election campaign. The OMA was publicly criticized by its parent organization, the AMA, for its neutral stand (M. O'Keefe, "AMA's National Board Opposes Measure 16," *The Oregonian*, October 22, 1994, p A1).

Although professional opposition now serves to oppose legalization of assisted suicide, it will send a mixed message to providers if physician-assisted suicide ever becomes legal. Physicians who have moral or ethical objections to assisted suicide will choose not to participate even if it is legal. Some physicians who might otherwise consider writing a lethal prescription for a dying patient may continue to consider it risky, even if it is legal, if it remains against professional guidelines. The risks might include not only professional disapproval or sanctions by professional organizations, but also privacy and personal safety. The recent targeting of physicians who perform abortions for demonstrations outside their homes and offices raises the possibility that similar tactics might be used against physicians who participate in assisted suicide.[9]

Hearing the Voters' Message

Just what are we to make of the Oregon electorate's approval of the Oregon Death With Dignity Act? We interpret the passage of the act as a mandate for urgent changes in the care of terminally ill patients.[10] Whereas proponents of the measure were motivated by the desire to make this option available to patients whose suffering they think could not be relieved by other means, we suspect that the narrow margin of victory reflects ambivalence and diverse motives among voters. Voters perceive important unmet needs in the care of dying persons. The public has been telling physicians for a long time that they too often abandon dying patients, exercise too much control over information and medications, inadequately treat emerging symptoms, and fail to respect refusals of treatment.[11] Voters clearly empathize with dying patients who suffer and are frustrated at the apparent inability of the health care system to address their needs. Their choice of physician-assisted suicide as an alternative is a statement of the degree to which physicians have failed to meet their needs or the needs of loved ones.

There is controversy in the professional literature about whether suffering can always be relieved by expert palliative care.[11,12] Regardless of whether physician-assisted suicide is legalized in Oregon or elsewhere, the health care community will need to define the appropriate professional standards to guide physicians in caring for patients with unrelieved suffering.

Hearing Patients' Message

To date, the debate about legalizing physician-assisted suicide has been framed in terms of morality, professional ethics, and patient rights. A largely unexplored aspect of this complex issue is the degree to which physicians feel up to the task of negotiating the issue with patients. As a professional group, physicians have no training in how to interview patients who come with a request for assisted suicide, no reliable information about what to prescribe, and only rare accounts of experiences with assisted suicide as a basis for incorporating it into practice (A. Solomon, "A Death of One's Own," *The New Yorker*, May 22, 1995, pp 5–69).[3,4,11,13]

Listening to and discussing end-of-life issues with patients is one of the most stressful interactions a physician can have, but also among the most rewarding. Many physicians are uncomfortable with these conversations, however, and patients are often dissatisfied by physicians' inadequate communication skills.[14,15] In Oregon, passage of the Oregon Death With Dignity Act has served as an incentive to rapidly enhance the training of medical professionals in the basic skills of interviewing, supporting, and providing comfort care to patients throughout the dying process.[10]

Whether or not an individual physician considers assisted suicide morally acceptable, there is considerable common ground for all physicians about how to approach a patient's initial request. Even for physicians who find any dialogue about assisted suicide inconsistent with their professional role, the AMA has recommended the following: "Requests for physician-assisted suicide should be a signal to the physician that the patient's needs are unmet, and further evaluation to identify the elements contributing to the patient's suffering is necessary."[16(p274)]

The first response could be to explore the patient's reasons for the request. This would require temporarily setting aside one's own values and actively listening to the patient's point of view. The patient's feelings about the process of dying, perhaps based on previous experiences with dying persons, could be explored. Does the patient fear pain, loss of control, dependency, or indignity?[4,17–19] The patient may feel overwhelmed, worthless,

or alone. Simply listening to the patient may help mitigate some concerns.[20] Some concerns may be treatable. A frank discussion between the physician and patient about how they will manage changing symptoms could result in a treatment plan that minimizes the potential for suffering and enhances the patient's sense of control.

The physician's initial response to the patient's request has the potential to leave the patient feeling supported or abandoned. A physician who conscientiously objects to writing a lethal prescription must eventually let the patient know; expressing objections too early, however, may prematurely truncate dialogue, causing the patient to feel more alone, rejected, and isolated. Conversely, if a physician whose philosophy might permit assistance in suicide fails to probe the patient's reasoning in depth, the ambivalent patient could inaccurately perceive that the physician agrees that suicide is the best alternative.

Contextual features will influence any physician's response to a patient's request for a lethal prescription. To each situation, the physician might bring moral or religious beliefs, concern about legal sanctions, or worries about social or professional ostracism or loss of privacy that might result from complying with a patient's request.[3,21] Interpersonal factors within the physician-patient relationship may also affect the physician's attitude toward prescribing a lethal medication. A patient who talks openly and asks questions about the course and timing of death may be perceived as devaluing the physician's skills.[21] A patient who is frightened and ambivalent about dependency may give conflicting messages regarding his or her true desires. The suffering that leads a patient to want an early death may also render him or her more irritable, contentious, and short-tempered. At the time the patient requests physician assistance with suicide, the physician may be emotionally distanced. At these moments, it is important for the physician to take stock of the relationship and redouble efforts to support the patient.

In many cases there could be an appropriate role for a mental health professional. The Oregon act requires that a psychiatrist or psychologist evaluate the patient if the primary physician suspects that a mental disorder may be affecting the patient's judgment. This model may undermine a mental health professional's ability to create a therapeutic alliance by its narrow focus on identifying psychopathology. The mental health professional could seize a possibly broader therapeutic role by exploring and challenging possibly rational decisions, offering support and guidance, exploring anger, and diminishing the patient's sense of aloneness.

Finally, developing good listening skills, promoting a deeper understanding of the patient's reason for such a request, and exploring the possibility of impaired judgment or depression take time. Health care systems must provide physicians adequate time to understand their patients' needs and to attend to them. The pressures of managed care and efficiency could hinder such a deep level of discussion. Physicians need to have supportive care of the dying legitimized by the establishment of appropriate reimbursement mechanisms. The Health Care Financing Administration's efforts to develop a diagnosis-related group for palliative care is a step in the right direction.[22] Physicians' skills in discussing and managing end-of-life issues should also be considered measures of quality of care.[23] These issues are too important to depend solely on individual physicians' personal responses.

Conclusions

The passage of the Oregon Death With Dignity Act in Oregon has profound implications nationally for the prevailing model of care for dying patients. During judicial review of the measure, the debate about physician-assisted suicide in Oregon has centered on how health care professionals can better provide for the needs of dying patients, including patients who request a lethal dose of medication. The Oregon Death With Dignity Act reminds physicians that they must become as competent in managing death as they are in treating disease. Indeed, the passage of the Oregon Death With Dignity Act may propel physicians to refine their approach to terminal care and to obtain the resources that dying patients need to relieve their suffering. These efforts are long overdue.

Acknowledgment

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Articles

Practice Environment for Nurse Practitioners in California

Identifying Barriers

ARLYSS L. ANDERSON, MHS, RN,CS, FNP; CATHERINE L. GILLISS, DNSc, RN,CS, FAAN; *and* LAURIE YODER, MN, MPH, RN,CS, FNP, *San Francisco, California*

Barriers exist that prevent nurse practitioners from using their primary health care knowledge and skills. We present the incidence of and specific barriers experienced by nurse practitioner respondents in California, the state with the largest number of nurse practitioners in the nation. A January 1995 survey was sent to all nurse practitioners certified in California to elicit their experiences regarding legal or social barriers in their practice, with space for an open-ended response. Of an estimated 3,895 nurse practitioners in California, 2,741 (70%) returned surveys. Most nurse practitioner (65%) respondents in California are providing primary care. Perceived barriers to practice are lack of prescriptive authority, lack of support from physicians, reimbursement difficulties, and lack of public awareness. Current barriers to nurse practitioner practice in California are similar to national barriers discovered in 1992 data. The development of interprofessional dialogue and the recognition of the contributions of all primary care professionals are some of the steps that can be taken to reduce these barriers and increase the use and effectiveness of nurse practitioners in primary care.

(Anderson AL, Gilliss CL, Yoder L: Practice environment for nurse practitioners in California—Identifying barriers. West J Med 1996; 165:209–214)

Estimates suggest that the United States will continue to have a shortage of primary care professionals well into the 21st century.[1] Increasing the use of nurse practitioners has been proposed as a solution to the lack of access to primary care services.[2–4] If nurse practitioners were used to their full potential, estimates suggest that they and other advanced practice nurses could save the United States 20% of primary health care costs[6] or between $6.4 and $8.75 billion annually.[7,8] The quality of nurse practitioner services has been documented to be comparable to the quality of physician care in the primary care setting,[8–16] with the addition of skills in prevention, access to community-based resources, health education, and counseling. The combination of lower cost of nurse practitioner education, the effectiveness and quality of their services, and the lower cost of employment provide compelling reasons for the full use of nurse practitioners in primary care. There is, however, wide variation in the use and scope of practice of nurse practitioners from state to state.*

The term "practice environment" was used in 1994 to describe the climate resulting from regulatory, social, and political influences on nurse practitioner practice. Favorable statewide practice environments have been positively associated with the supply of nurse practitioners.[17] Practice environment scores for each state were determined based on the legal status of the profession, the reimbursement of services, and the authority to prescribe.

When compared with other states, California has rated poorly as a practice environment for nurse practitioners, earning only 30 of 100 points (30.2 points below the mean) and ranking 46th of 50 states. A study by Wilken found that the amount of state effort that is put forth to develop programs and funding for nurse practitioner education, the number of educational programs in a state, the authority to prescribe, and direct third-party reimbursement were significant predictors of the availability of nurse practitioners.[18] Barriers such as the lack of prescribing authority and reimbursement difficulties prevent nurse practitioners from providing the comprehensive care for which they have been trained. Yet, little is known about the current perceived practice environment and particularly the barriers that nurse practitioners face in California. With the largest total number of nurse practitioners in the nation, California is an important

*See also the editorials, "Physicians and Nurse Practitioners—Old Conflicts and New Opportunities," by L. J. Finocchio, MPH, J. M. Coffman, MPP, C. M. Dower, JD, and E. H. O'Neil, PhD, on pages 246–248 and "Barriers to Practice—Reality or Perception?" by K. M. Tait, MD, and R. J. Patchin, BSN, MD, on pages 245–246 of this issue.

From the Department of Family Health Care Nursing, University of California, San Francisco (UCSF), School of Nursing.

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Reprint requests to Arlyss L. Anderson, MHS, RN, CS, FNP, Dept of Family Health Care Nursing, UCSF School of Nursing, N411-Y, Box 0606, San Francisco, CA 94143-0606.

ABBREVIATIONS USED IN TEXT

BRN = Board of Registered Nursing
HMO = health maintenance organization
MD = physician
NP = nurse practitioner

state to study. We report the incidence of and specific barriers currently perceived by California nurse practitioners.

Methods

As part of a survey to create the first database on nurse practitioners certified by the Board of Registered Nursing (BRN) to practice in California, the California Nurse Practitioner Database attempted to contact by mail the 5,500 nurse practitioners certified by the BRN as of July 1994. The survey, mailed in January 1995, focused primarily on current demographics of nurse practitioners and nurse practitioner practice characteristics in the state of California. In addition, questions were asked regarding their practice environment. In particular, did they experience social or legal barriers to practice, and what were these? The answer was left open-ended, rather than comprising specific lists, to permit a breadth of responses and to have respondents' own words to detail barriers. Although more complex to analyze, open-ended responses have the potential of providing richer data.

Questionnaires were returned from 2,741 nurse practitioners, with 387 undeliverable returned surveys. Due to the anonymity of responses and funding limitations, nonresponders were not contacted. Although the current number of nurse practitioners in California is not known, a 1993 study estimated the number at 3,895, adjusting for those with dual state licensure.[19] Based on this estimate, the response rate is calculated to be 70%. Because the BRN listing of 5,500 certified nurse practitioners includes all who have ever been certified and has not been well maintained, it is likely a less reliable measure of how many nurse practitioners are currently in California.

The data were coded equally by two of us (A.L.A. and L.Y.) and analyzed using the Crunch 4 Statistical Package.[20] Univariate analytic approaches were used to describe the sample and the results. In response to the open-ended question regarding legal and social barriers to practice, the coders independently compiled a verbatim list of comments. Then, as a team, the coders developed key categories from the independent lists and collapsed the comments into the thematic categories discussed later. Few disagreements occurred in placing the comments into categories; the disagreements that did result were discussed between the coders until agreement was reached.

The thematic categories were shared with an expert panel of practicing nurse practitioners, consisting of two family nurse practitioners and a pediatric nurse practitioner, all with extensive practice experience in various settings. None of the expert panel members disagreed with any of the thematic categories. As the coders noted, these nurse practitioners fully recognized the themes from their own practices, having experienced similar barriers. In addition, the expert panel members expressed feeling frustrated and discouraged by the results of the survey. This finding was consistent with the coders' initial reaction to the overwhelmingly disheartened tone of many of the survey respondents' comments.

Results

Among the reporting 2,741 nurse practitioners, the largest specialty training group was the family nurse practitioners (n = 1,089, or 40%), followed by those in women's health (n = 677, or 25%), pediatrics (n = 516, or 19%), adult (n = 490, or 18%), family planning (n = 323, or 12%), geriatrics (n = 189, or 7%), schools (n = 99, or 4%), certified nurse midwives (n = 104, or 4%), occupational health (n = 88, or 3%), and psychiatry (n = 33, or 1%) (total percentage >100 as some of the NPs are prepared in more than one specialty area). Most were prepared in certificate programs (52%), although the majority (57%) held a master's or higher degree. Most were employed in primary care (65%), and most were employed full time (57%). The sample was predominantly female (96%), white (85%), and middle-aged (65% ages 41 through 60 years). Most identified themselves as practicing in urban areas (53%), followed by suburban (33%) and rural (10%) settings.

Of those answering the question, "Do you experience legal or social barriers to your nurse practitioner practice?" 43% (n = 1,081/2,493) responded "yes." In this survey, nurse practitioners working in correctional facilities reported the highest frequency of barriers (61% [49/31]) as well as those practicing in rural areas (61.3% [49/80] of those whose second practice was in a rural area, and 49.1% [115/234] of those whose primary practice was in a rural area). Additional space was provided for specific barriers to be listed. Barriers were described by 829 responders with some responders citing more than one barrier. The data reduction resulted in four broad categories (Table 1):

- Lack of ability to prescribe medications,
- Lack of support by physicians,
- Reimbursement difficulties, and
- Lack of public awareness of the role of the nurse practitioner.

There was no significant association between practice site and barriers detailed. The barriers appear to cross practice-site categories.

Lack of Ability to Prescribe Medications

The limitation of prescribing privilege (Figure 1) was by far the most frequently reported barrier, with 415 handwritten comments.[21] Representative comments included the following: "No true prescriptive authority or incomplete prescriptive authority"; "no prescriptive rights"; "restrictions on prescribing in nursing home, school, correctional facility"; "unable to prescribe nar-

TABLE 1.—*Specific Barriers to Practice Perceived by Nurse Practitioners*

Thematic Category	*Respondents, No.*	*Total Comments, %*
Lack of prescribing authority	415	45
Lack of physician support	175	19
Reimbursement difficulties	118	13
Lack of public awareness	111	12
Miscellaneous	94	10
Total	917	100

cotics"; "NP [nurse practitioner] name not listed on bottle—patients are confused"; and "too many restrictions."

Lack of Support by Physicians

A lack of support describes a wide range of concerns. Of the 175 comments in this area, the most common was "MD [physician] discrimination against NP practice," and "lack of acceptance by MDs." Additional comments ranged from "MD intimidated and/or threatened by NP practice," "direct opposition from MD against NP practice," "MDs against hospital privileges," "MD resistance, slow to accept role in this community," to "MDs have strong monopoly," "MD unwilling to relinquish control and allow autonomy of NP as a professional," "refusal of specialists to accept referrals," "difficult to get MD supervision or backup," and "lack of support."

Reimbursement Difficulties

Difficulties with obtaining payment for services rendered or planned exclusion from reimbursement pose serious obstacles to nurse practitioner practice. Representative comments from the 118 received included "lack of uniformity in third-party reimbursement," "Medicare and Medi-Cal [California's Medicaid] restrictions on reimbursement," "low levels of reimbursement," "paid less than regular RN [registered nurse]," "insurance companies unwilling to permit capitated reimbursement to NPs," "provider panels closed to non–MDs," and "unable to be paid at all in managed care, capitated system."

Lack of Public Awareness

The public's limited understanding of the role of nurse practitioners appears to mirror the understanding held by the physician community. Many of the 111 comments falling into this category related the fact that patients are not accustomed to dealing with a provider who is not a physician. Comments included "lack of community awareness of role," "lack of public understanding of role," "seen as 'second rate' medical service," and "prejudice because not MD."

Discussion

The practice barriers for nurse practitioners found in this study of a lack of full prescribing authority, lack of support from physicians, reimbursement difficulties, and lack of public awareness have also been found in a 1992 national survey of certified nurse practitioners (California, 192; national, 1,378) and clinical nurse specialists.[22] In response to a predetermined listing of barriers in that study, the same categories were rated as important, although the order in which the barriers were ranked was different. In the national survey, the first choice on the list, "limitation of space of facilities," outweighed any of the others and did not appear in the California survey, which requested social or legal barriers. The national survey found that when given a long list of possible barriers, 99.5% of practicing nurse practitioners experience one or more barriers to practice. Another smaller survey, also employing a predetermined listing of barriers and conducted in California in 1993 by the California Coalition of Nurse Practitioners (n = 277), found similar concerns, with the barriers ranked as follows (J. Morrow, "NP Survey Results," *California Coalition of Nurse Practitioners Newsletter*, March-April 1994, p 3):

- "Not identified as a provider by private insurance,"
- "Lack of prescriptive authority,"
- "Lack of insurance reimbursement," and
- "Restrictions on scope of practice."

Although the public awareness issue did not appear in these data (it was not included in available options), it did appear when respondents were asked to list areas for organizational activity according to their importance. Public relations and media coverage were ranked fourth, with the first three concerns the same. The concern over lack of physician support did not appear because it was not included as an option. Attitudes and perceptions of the medical community were seen as the most important

California is 1 of 45 states that has prescriptive privileges for nurse practitioners. 11 states permit independent nurse practitioner prescribing, including of controlled substances, and 20 more states permit controlled-substance prescribing in collaboration with a physician. California law, however, allows only "furnishing" of medications and devices in accordance with a standard procedure and physician collaboration. These privileges are available to only those who are certified as nurse practitioners in the state, who have completed 30 hours of additional pharmacology training, and who have been supervised by a physician for 6 months and found to be capable of safe "furnishing" of medication, as determined by the physician. The nurse practitioners may then use a "transmittal order," which looks like a prescription, with the supervising physician's name as well as the "furnisher's" name on the order. In addition, these medications or devices are to be used "incidental to the provision of family planning services, perinatal services, or routine health care to essentially healthy persons."

Figure 1.—California's current prescribing practice environment for nurse practitioners is described.[21]

barrier to the practice of certified nurse midwives in a recent national study.[23] Although the order of importance of barriers may differ from state to state, it appears that the barriers relating to prescribing authority, physician opposition, reimbursement, and public awareness are consistently seen in the California and national data.

Lack of Full Prescribing Authority

Nurse practitioners in California have been shown to have excellent "furnishing" performance.[24] Site restrictions in the current furnishing act in California prevent nurse practitioners from "furnishing" in correctional facilities, psychiatric facilities, rehabilitation facilities, schools, and nursing homes,[21] sites that, arguably, could use nurse practitioners and often have difficulty retaining physicians. Ironically, a patient seen in a clinic setting may be given medication by a nurse practitioner for her diabetes, but the same patient could not be served in a nursing home or other noncovered setting. Within the restricted sites, a physician must prescribe the medication.

The furnishing act also limits the categories of medications a nurse practitioner may furnish. Most pain medications and other controlled substances are excluded. The inability to furnish specific classes of drugs, such as controlled substances, limits the use of nurse practitioners, for example, in hospice care where pain medications are crucial to the care of patients with terminal illness. These restrictions also prevent nurse practitioners from using cough preparations with codeine or pain medications for acute injury. Although the concern about abuse is a commonly cited reason for limiting their inclusion, in a recent telephone survey of state boards of nursing, the boards reported that few disciplinary actions for misprescribing had been taken against nurse practitioners (J. Morrow, "National Report Card for NP Prescribing," *California Coalition of Nurse Practitioners Newsletter*, November-December 1995, p 5). Despite the fact that some states have a 20-year history of nurse practitioner prescribing, no state reported more than three disciplinary actions in recent years, and many states reported that no actions had been filed.

Increasing the number of nurse practitioners in rural areas may be directly related to an increased ability to prescribe medications. The number of rural health clinics quadrupled in Texas after physician assistant prescriptive legislation passed in 1991, and the percentage of PAs practicing in rural areas increased from 5% to 15%.[25] If state policymakers are interested in containing health care costs and increasing access to primary care services, increasing the prescribing authority for nurse practitioners is an area where they could have major influence.

Lack of Support by Physicians

It has been suggested that professional barriers such as the lack of support by physicians can be viewed largely as the result of either a lack of information or bias.[26] Although recent educational efforts have attempted to cotrain physicians, nurse practitioners, and other nonphysician professionals in primary care training programs, few physicians have had contact with nurse practitioners or understand their experience, training, and education. Without this background, physicians will seldom be supportive.[15,26] The comments from nurse practitioners that referrals to community specialists are difficult may be related to this lack of contact. In a recent survey conducted by Blue Cross and Blue Shield of California, 61% of nurse practitioner respondents (n = 2,752) thought that the role was totally accepted by the physicians in their practice site, but only 12% thought that the role was totally accepted by physicians in the community ("Nurse Practitioner Survey," *Intelliscan*, 1995). The development of referral networks supportive to nurse practitioners in areas where there is a choice of specialists and increased interprofessional communication are necessary to provide continuity and well-coordinated services to the public.

The issue of bias between physicians and nurses is long-standing and has been well described.[27,28] Effective communication between these two groups on an organizational level has been difficult. Using the theories of Jürgen Habermas, a recent analysis of physician-nurse communication suggests that ideal communication may not be achievable when two groups are so asymmetric. In the current hegemonious political and economic structure, an atmosphere of repression may be present.[29] This asymmetry must be acknowledged if effective communication is to occur. The communication difficulties and "turf battles" are complicated by issues of sex, social class, and cultural biases. Today, in a fiercely competitive health care system, the struggle is further complicated by economics.

While the team was coding the data, it noted an overall disheartened tone in the comments made by respondents. This was independently observed and experienced by each coder and later validated between coders. Comments such as "NP participation prohibited," "not able to use knowledge fully," "refusal of specialists to accept referrals," and "excessive regulation" all relate to a sense of being restrained, held back, or excessively controlled—signifying repression. This language reflects the problem and no doubt contributes to its continuation.

Nurse practitioners have been trained to work collaboratively with physicians, and in California, 97% do. Working in collaborative practice arrangements can extend the reach of professionals into communities where care is needed and increase the breadth of services offered by the practice.[30] Many models have been used with differing levels of collaboration between nurse practitioners and physicians.[28] Sharing competency domain where there is overlap and valuing and respecting contributions from other professionals where functions are complementary would permit greater movement toward the shared goal of increased access to high-quality, comprehensive, and affordable health services for the public. A former president of the American Medical Association, Palma Formica, MD, recently stated:

"Primary care is most cost-effective when delivered by nurse-physician teams. Mutual respect, collaboration, and cooperation between [nursing and medicine] professions will ensure the highest quality care."[31(p20)]

Reimbursement Difficulties

After modest gains were made in reimbursement to nurse practitioners in 1992 and 1993 by Medicare, Medicaid, and private insurers, California moved to a capitated system in many managed care programs, including Medi-Cal. Providers are paid on a per capita basis, but the only primary care professionals included in the reimbursement arrangements are physicians. Names of nurse practitioners cannot be published in provider directories to show that a nurse practitioner is in a practice, nor are nurse practitioners included in the provider panels accepted by insurance companies. One nurse practitioner working in a rural area who has been providing care to thousands of people is now unable to be paid for her services unless she is paid by a physician (L. Scudder, "Independent Nurse Practitioner Shut Out by Managed Care," *Nurse Practitioner News* 1995; 3:1). Nurse practitioners who were employed by physicians and groups have found that they are no longer paid by insurers for the care they provide. For salaried nurse practitioners in health maintenance organizations (HMOs) or large organizational settings, methods of reimbursement may not have changed much. For those in non–HMO settings where third-party reimbursement is the basis for wages, this change may be dramatic.

The Wilken study found that direct third-party reimbursement was a significant predictor of nurse practitioner availability.[18] The high perception of barriers by rural nurse practitioners, as well as the low number of nurse practitioners providing rural health care, may be related to the fact that rural and migrant health centers hire only nonphysician health care professionals whose services will be reimbursed.[32] Provider panels that include nonphysician providers and that permit the reimbursement of these professionals is an important change in the current "managed care" system. We need further development of reimbursement mechanisms to adequately and equitably compensate nurse practitioners for their patient care responsibilities.

Lack of Public Awareness

The role and name "nurse practitioner" are relatively new (30 years) and not well understood. In some cases, the actual name is not easily translated into other languages to convey the difference between this type of nurse and any other. Although studies show high levels of patient acceptance,[15] there are relatively few active nurse practitioners in California compared with physicians (approximately 4,400 nurse practitioners and 70,000 physicians).[19] Increased news media exposure and continued exposure of the public to nonphysician primary care professionals will help to alleviate this barrier.

Limitations of Study

The major limitation of this study was the lack of nonresponder follow-up, effectively creating a response bias. In addition, the coders and expert panel were all nurse practitioners, which may cause interpretation bias. The sample was drawn from California nurse practitioners, which, in addition to response and interpretation bias, limits the generalizability of the study. Further study of this group would be helpful to determine practice site characteristics that permit an appropriate use of the nurse practitioner role and have the least barriers. Although not undertaken in this study, an evaluation of the effect of managed care on barriers to nurse practitioner practice would be helpful in today's market.

Conclusion

The practice environment for nurse practitioners in California is perceived by them as being substantially influenced by four factors: lack of full prescribing authority, lack of support by physicians, reimbursement difficulties, and lack of public awareness. Overly restrictive regulations governing prescribing authority can be altered with commitment from state and federal policymakers and cooperation from medical lobbies. State and federal efforts to provide funding for training programs are also necessary to increase the availability of nurse practitioners. Although attitudinal changes and the removal of bias are never easy, developing effective interprofessional and interorganizational dialogue and valuing and respecting each profession's contributions are important beginnings. Reimbursement systems must be developed that include nurse practitioners as reimbursable professionals whether or not they are directly employed by an organization or a physician. Informational programs aimed at increasing public awareness of the expanded role of nurse practitioners are needed. The goal of high-quality, affordable, comprehensive primary care services presents a formidable challenge to all health care professionals. We cannot afford to have barriers that prevent the full use of competent, cost-effective, primary care professionals.

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Conferences and Reviews

Prognosis and Treatment of Burns

ROBERTA MANN, MD, *and* DAVID HEIMBACH, MD, *Seattle, Washington*

Survival rates for burn patients in general have improved markedly over the past several decades. The development of topical antibiotic therapy for burn wounds, the institution of the practice of early excision and grafting, and major advances in intensive care management have all contributed to this success. In this review we address these 3 important advances in the modern treatment of burn injuries and provide a brief historical overview of these accomplishments and others, emphasizing specific achievements of note and promises for the future. We also discuss 3 topics of interest to burn physicians, including the special problems and high mortality of elderly burn patients, the disturbingly high mortality in burn patients with inhalation injury, and the possible use of artificial skin to facilitate rapid wound closure.

(Mann R, Heimbach D: Prognosis and treatment of burns. West J Med 1996; 165:215–220)

The progress that has been made in burn care over the past four decades has dramatically increased survival rates for burn victims.[1,2] The advances that led to this success accompanied the following three giant steps in the history of modern burn care:

- The introduction of topical antibiotic therapy into the wound care armamentarium;
- The adoption of the technique of excising the burn eschar of large burns; and
- Improvements in the technology and clinical skill in the management of burn wounds, resuscitation, and nutrition and the prevention and management of associated pulmonary problems.

These three areas of clinical advancement have merged to produce an LA_{50} of 70% (half of patients with 70% of the total body surface area burned will survive) compared with an LA_{50} of less than 50% in 1952 (Figure 1).[3]

In this review, we address the three most important advances in the modern treatment of burn injuries. The contribution to improved mortality made from these three giant steps has changed the prognosis of burn injuries substantially. Next, we provide a brief historical overview of the progress of mortality of burn injuries. Finally, we discuss three topics of interest to those who routinely care for patients with burns, including the special problems and high mortality of elderly burn patients, the disturbingly high mortality in burn patients with inhalation injury, and the possible use of artificial skin for facilitating rapid wound closure when donor site healing is problematic.

Three Giant Steps

Topical Antibiotic Therapy

Safe, effective topical antimicrobial therapy for burn wounds was first introduced in the mid-1960s.[4] By the early 1970s, decreased mortality was reported in burn patients treated with topical antibiotic therapy.[5–7] Over a ten-year period, the treatment of burn wounds with either 0.5% silver nitrate solution, mafenide acetate cream, or silver sulfadiazine cream became the standard method of care for controlling the microbial environment of burn wounds. The limitations of topical antibiotic therapy were discussed in 1974, when it was observed that all topical agents are roughly similar in their ability to control burn wound sepsis and that all reduce mortality by about the same degree.[8] Furthermore, the development of topical antibiotic therapy for burn wounds served more to delay the onset of wound sepsis than to prevent it, and the benefits applied to only small and moderate-sized burns, with seemingly no effect on the mortality of massive burns. At the same time, these drawbacks were specifically addressed with the introduction of a technique of primary burn wound excision, and a convincing argument was made about why burn eschars should be separated from the healing wound. The plan was to develop a system of burn care that is directly based on the surgical principle of immediate debridement of necrotic tissue and primary wound closure.[8]

Primary Excision and Grafting of the Burn Wound

The first favorable report of the use of primary excision of burn wounds came in the mid-1940s, in the aftermath of the Boston, Massachusetts, infamous Coconut Grove fire.[9] The technique did not merit high acclaim during the 1950s, however, because of clinicians' limited ability to support the huge metabolic demands that inevitably accompanied the procedure.[10,11] In fact, in 1960 the procedure fell into disrepute when the cases of 25 patients with large burns who underwent fascial excision and grafting were compared with those of patients

From the Department of Surgery, University of Washington School of Medicine, and the Burn Center, Harborview Medical Center, Seattle.
Reprint requests to Roberta Mann, MD, Harborview Medical Center, 325 Ninth Ave, Box 359796, Seattle, WA 98104.

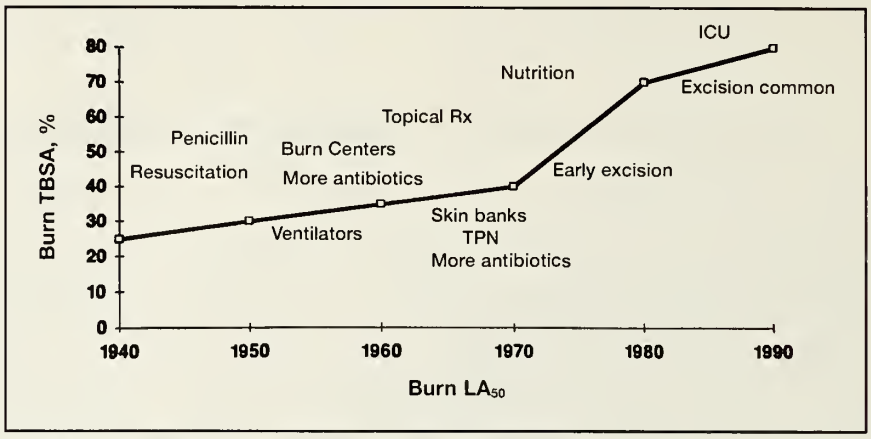

Figure 1.—A schematized time line of important advances in burn care is shown. ICU = intensive care unit, LA_{50} = survival of half of patients, depending on the percentage of total body surface area (TBSA) burned, Rx = therapy, TPN = total parenteral nutrition

who had delayed grafting and grafting on granulation tissue. Mortality was not increased, but neither was it decreased, thus safety if not effectiveness was ensured.[12] In 1970, concurrent with pronounced advances in critical care management of burn patients, the concept of early excision and grafting was reintroduced with a classic description of the tangential excision procedure.[13] In 1974, improved survival and a shorter time to wound closure were reported in patients with burns of 10% to 65% of total body surface area when treated with excision and grafting (with silver nitrate dressings) versus silver nitrate alone.[8] In 1988 the mortality of children with burn injuries was substantially reduced through the use of prompt eschar excision.[14] In 1989 patients were randomly assigned to receive either early excision or topical antimicrobial therapy and skin grafting after spontaneous eschar separation. Mortality from burns without inhalation injury was decreased by early excision from 45% to 9% in patients who were 17 to 30 years of age ($P < .025$).[15] These and many other studies confirm the improvements in survival and decreased length of hospital stay that can be achieved with the practice of early excision, even for large burns.

Advances in Technology and Clinical Skill

Although the practice of early excision and grafting has had considerable effect on survival for patients with massive burns, other factors have contributed substantially to its success. These include the somewhat intangible gains in clinical insight that come from years of experience in caring for burn patients. More tangible factors include advanced intensive care unit monitoring and nursing protocols, better ventilators, and better skill in surgical departments. In one series, the cases of 57 adults patients with massive burns (≥50% of total body surface area) from 1980 to 1989 were compared with those of 56 patients with similar massive burns in the period between 1970 and 1979. The results show a significant improvement ($P < .01$) in the survival rate of the more recent patients, attributed to improvements in the early treatment of inhalation injury, sepsis, and multiorgan failure.[1] The cases of 15 patients from 1978 to 1979 were compared with those of 16 patients treated in 1980 to 1981. Early excision was practiced in both groups, but during the first week in the later group. Factors noted to contribute to improved survival were early endotracheal intubation with the application of positive end-expiratory pressure before evidence of pulmonary dysfunction; the elimination of Swan-Ganz and central venous lines for early volume restoration unless absolutely necessary; the addition of hypertonic saline solution and protein infusions during the first 24 hours of resuscitation along with Ringer's lactate alone, resulting in a 30% decrease in fluid requirements; the rapid institution of nutritional support beginning day 3 using a combination of peripheral hyperalimentation and tube feeding; and early eschar excision and grafting beginning in the first week rather than the second or third week, as previously practiced.[16] General improvements in the management of critically injured patients have contributed substantially to the improved mortality rates of burn patients.

The benefits and limitations of burn wound excision were discussed in 1992, when the technique was viewed in the larger context of the total care and rehabilitation of patients with burn injury. Several factors were named that may have contributed to the decreased mortality seen after the institution of early excision and grafting, including improved antibiotic regimens, improved modes of ventilatory support, and improved methods of managing the postburn hypermetabolic response, such as better nutrition. It was also stressed that the benefits of excisional therapy lie not in the excision itself, but in the ability to accomplish rapid wound closure with skin grafts. Attention was called to the major unresolved problem in burn wound care today: the unsatisfactory appearance and functional impairment that may attend the scars of deep burns.[17]

Historical Overview of Burn Mortality

The most important factors associated with mortality,

namely, patient age and extent of burn, have not changed. As early as 1902, it was shown that the survival of burned patients was related to patients' age and extent of total body surface area burned.[18] In 1961 the prognostic value of the simple addition of age plus the percentage of burn surface area was shown. Although this finding was not published in the surgical literature, it gained wide acceptance and became the most common method used in predicting mortality in burn patients.[19] In 1982 other factors were found that substantially influence survival, including the admission leukocyte count, admission serum osmolality, the involvement of inflammable liquid, and the presence of preexisting mental disorders, circulatory disease, and digestive disease.[20] Still other factors found that significantly affected survival in a series of patients included the arterial pH and serum protein concentration at the beginning of treatment.[21] Despite these later attempts to better identify patients at high risk of dying, it was again shown in 1991 that mortality from burns was directly proportional to the extent of injury and the patient's age.[22]

In the 1960s, burn shock was the leading cause of in-hospital death after major burns.[23] Due to the release of neuroendocrine factors at the time of injury, extensive burns evoke circulatory derangements at both local and systemic levels, which may quickly lead to cardiovascular collapse.[24] The term "burn shock" describes the rapid onset of circulatory failure that occurs over the first 72 hours after injury if inadequately treated. The most important breakthrough in the successful management of burn shock proved to be the discovery that the expeditious administration of fluid could prevent its disastrous course.

In 1923, after the cases of 21 victims of the 1921 Rialto Theater fire in New Haven, Connecticut, were analyzed, it was noted that burn shock was due to intravascular fluid loss.[25] Since then, debate has raged over the optimal fluid resuscitation regimen to be used to prevent burn shock. The 1978 Consensus Development Conference on burn care issued a statement that fluid restoration in the first 24 hours should be with a balanced isotonic salt solution such as Ringer's lactate, that such a solution was as effective as colloid-containing fluids for the initial resuscitation, that colloid was of value in the period beginning 24 hours after a burn, and that the complete restoration of plasma volume as soon as possible after capillary leakage was resolved was beneficial.[26] As a result, burn shock is now prevented or reversed in 70% to 95% of cases when applied in a burn referral center.[27,28]

As the pathophysiology of burn shock was finally being understood and conquered, infection became the great killer of burn patients. The "conservative" method of burn wound management that was widely used consisted of topical antimicrobial therapy until spontaneous eschar separation, followed by autografting. Eschar separation is caused by the process of bacterial enzymatic digestion at the surface of the wound. Although topical antibiotics are helpful in maintaining microorganism counts below an invasive level, they also slow the natural process of eschar separation by decreasing the concentration of enzymatic lysins available in the wound. Morbidity is prolonged as weeks are spent waiting for the eschar to separate and fall off so that skin grafts can be placed on granulation tissue. Furthermore, even though the burn wound itself may remain free of invasive infection, the eschar remains present as a source of seeding to other vulnerable areas, particularly the respiratory tract. In 1962 respiratory tract damage was targeted as the principal killer of burned patients.[29] This was confirmed in 1970 when it was shown that pulmonary sepsis was the principal cause of death among a series of burn patients.[30] In 1979 late infectious complications were reported to have supplanted circulatory collapse as the leading cause of in-hospital death.[31] These late infectious complications are more commonly from a pulmonary source than from the burn wound itself.

In summary, a comprehensive review of the literature reveals that in 1996, the major factors associated with mortality in burn patients are age and percentage of total body surface area burned. The presence of inhalation injury and comorbidity are other crucial factors. Early excision and grafting have supplanted conservative management as the recommended treatment of large burns, except perhaps in elderly patients.[32] The fatal consequences of pulmonary complications are emphasized in the literature, and aggressive methods of pulmonary management are recommended.[33]

Special Considerations

Elderly Burn Patients

Older adults (in general, those older than 60 years) constitute a special population of burn patients. For any given burn size, their mortality is higher than for younger persons. Older patients have decreased physiologic reserve, which renders them less able to tolerate the metabolic demands of serious injury.[34] The thinner skin of older adults leads to larger and deeper burns and deeper donor sites. Delayed donor-site healing is a major cause of postburn morbidity in older patients that is related to an age-dependent slow rate of epidermal proliferation.[35] The threat of pneumonia is ever present in older patients and has been shown to be a significant factor affecting mortality in all burn patients.[30] Impaired senses and slow reaction time—often the factors that cause the injury in the first place—contribute to the difficulty in managing the logistics of wound care and activities of daily living for these patients. Older people who were living alone when they were injured seldom return to their former level of functioning and commonly require alterations in living arrangements, a situation that can be psychologically devastating to burn survivors.

In 1955, it was noted that there were no reports of patients older than 60 years surviving with greater than 10% burns.[36] Sixteen years later, it was again noted that no patients older than 60 years with burns over greater than 30% of the total body surface area survived.[37] In a

series of burned aged patients, survival was improved with the use of 0.5% silver nitrate solution. In 1983, the concept that adequate urine output is an indicator of adequate volume status during burn resuscitation, especially in elderly patients, was challenged. It was concluded that physiologic profile monitoring (pulmonary artery catheterization) in older patients is a useful guide to the precise management of fluid restoration and the early detection and treatment of ventricle dysfunction and that these result in improved survival.[38] In 1995, the mortality of a group of 111 octogenarians was reported to be 26%, the patients on average faring better than their predicted mortality rates as derived using either the Baux Index, the Bull Table, or the Abbreviated Burn Severity Score.[39] This improvement in mortality has not been reported elsewhere, however, and the literature suggests that survival rates have not improved substantially over the past 20 years in elderly patients with large burns.[40]

There is a positive note regarding the outcome of elderly burn patients. In 1992, decreased mortality was reported in patients older than 65 years at a burn center, achieved by increasing the number of nurses, changing local burn wound treatment, improving the documentation of wound status and general conditions, and improving nutritional support. As the general population ages, more experience is gained in the management of the special problems of older patients. Literature reports compare traditional with nonstandard treatment methods to ensure that results improve.[32,41,42] Social and rehabilitation services have become standard components of burn care for elderly patients and provide more today in the way of services and facilities than ever before. The stage is set for making noticeable improvements in the mortality of older burn patients. Because older patients often survive the resuscitation phase only to die of complications during the prolonged wound healing phase, early wound closure with artificial skin may indeed prove lifesaving for these vulnerable patients.

Inhalation Injury

As many as a third of patients with major burns have associated inhalation injury, often a lethal concomitant insult to otherwise less serious burn injuries.[43] In 1973, investigators labeled inhalation injury as the major threat to burn patients. In a series of 100 patients with smoke inhalation, pulmonary complications developed in 22, with 86% mortality.[44] In a review of the literature in 1981, it was concluded that inhalation injury was still a primary determinant of survival following major burns.[45] Further literature reviews in the 1990s confirmed the fact that not much progress has been made in improving the survival rates of patients with smoke inhalation in combination with major burns.[46]

Inhalation injury may be described as an acute respiratory tract injury caused by steam or toxic inhalants such as fumes, gases, or mists.[47] Thermal inhalation injuries per se are rare due to the efficient cooling mechanisms of the respiratory tract. Severe chemical injuries from smoke inhalation are common, however, due to the caustic nature of incomplete products of combustion that are released by burning compounds.[48] The extent of inhalation damage depends on the composition of the burning material, the concentration of fumes given off (whether in a closed space or not), the temperature of the gases (rarely an important component), and the duration of exposure of the patient to the caustic fumes. The result is some degree of tracheobronchitis.[49] In severely affected patients, tracheobronchial mucosal slough and airway obstruction from cellular debris subsequently develop, followed by pneumonia and the potential for invasive sepsis. The burn induces inflammatory cascades that result in pulmonary leukocyte and macrophage activation, thereby worsening the injurious effect on the lungs. This inflammatory response persists until final wound closure is achieved.

Optimism is expressed in the literature that mortality for patients with combined burn and inhalation injuries is improving. Much of the credit is attributed to general advances in intensive care management, improved infection control measures, and better antibiotic combinations for the treatment of pneumonia. Improvements in the ventilatory management of these patients have been shown with the use of high-frequency ventilation[33] and extracorporeal membrane oxygenation, a treatment method that has shown promise in children with burns.[50]

Carbon monoxide toxicity is a type of inhalation injury that deserves special mention, as it is one of the leading causes of deaths from fires.[51] Carbon monoxide is a tasteless, odorless, and colorless gas with an affinity for hemoglobin 200 times that of oxygen. As oxygen is consumed during the burning process, carbon monoxide is released. It then binds preferentially to the hemoglobin molecule in place of oxygen, shifting the hemoglobin-oxygen saturation curve to the left and resulting in major impairments in oxygen delivery. The goal of the treatment of carbon monoxide toxicity is the total displacement of carbon monoxide on the hemoglobin molecule by oxygen as early as possible (the half-life of carboxyhemoglobin is 30 minutes in a patient breathing 100% oxygen) to prevent devastating neurologic sequelae (anoxic brain injury). Oxygen is usually administered in concentrations of 90% to 100%. Hyperbaric oxygen (2 to 3 atm) produces an even more rapid displacement of carbon monoxide and may be useful when exposure has been extensive. Although hyperbaric oxygen therapy is commonly used for persons who have sustained carbon monoxide poisoning without burn injury, there is less acceptance of its use in patients with considerable burns.[52–54]

Skin Substitutes

Burn specialists continue to await the development of the ideal skin substitute. Cultured epithelial autografts, at one time thought to be the answer to the wound coverage problem,[55] have proved to be disappointing. They have been presented as lifesaving therapy,[55] but long-term results have not yet been reported. Furthermore, recent reports of the use of these allografts describe poor

graft take when used for the treatment of massive burns.[56,57] The lack of dermis available beneath these thin autografts prevents the development of sturdy skin. The result is a fragile scar surface that bears little resemblance to normal skin for many months. This situation was described histologically in 1988.[58] The use of these autografts for smaller or shallower burns is an avenue that remains to be explored and one in which cost-effectiveness analyses are critical.

In a 1988 multicenter randomized clinical trial, increased survival was reported in patients with life-threatening burns, associated with the use of artificial skin.[59] Two years later, a histologic study of the product the investigators in that study used, now called Integra, was published.[60] Integra consists of a dermal substitute of bovine collagen and chondroitin-6-sulfate and an epidermal layer of synthetic polysiloxane polymer (Silastic). It was reported that with rare exceptions, an intact dermis was achieved as well as definitive closure of a complete epidermal layer with a minimum of scarring. Integra is now available for clinical use, and the results of clinical studies are anticipated. Many synthetic products have been developed as skin substitutes, but their clinical efficacy and cost-effectiveness have yet to be established.[61–63]

Conclusions

We have presented a brief overview of the accomplishments made in burn therapy over the past several decades. The following conclusions can be drawn from the preceding review:

- Pronounced improvements have been made in the mortality statistics of burn patients in general over the past several decades. The LA_{50} is currently 70% of the total body surface area.
- Infectious complications, mainly pulmonary, have supplanted burn shock as the main killer of burn victims.
- Early excision and grafting have replaced conservative management as the recommended method of treating large burns, except perhaps in elderly patients.
- Despite a revolution of advances in critical care medicine and surgical treatment, burn patients older than 60 years and those with inhalation injury continue to have disproportionately high mortality.

The development of a satisfactory skin substitute is on the horizon. Measures of success must include clinical effectiveness in achieving wound closure and cost-feasibility studies.

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Epitomes

Important Advances in Clinical Medicine

Preventive Medicine and Public Health

Ronald P. Hattis, MD, MPH, and Richard Hart, MD, DrPH, Section Editors

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in preventive medicine and public health. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Preventive Medicine and Public Health of the California Medical Association, and the summaries were prepared under the direction of Ronald P. Hattis, MD, MPH, Richard Hart, MD, and the panel.

Epidemiology and Control of Coccidioidomycosis in California

COCCIDIOIDOMYCOSIS IS a fungal disease endemic principally to certain parts of the southwestern United States and northwestern Mexico and caused by *Coccidioides immitis*. The disease was first described in Argentina in 1892, but it was during the dust bowl migrations of the 1930s that the full clinical spectrum of coccidioidomycosis and its importance as a public health hazard for Californians residing in the southern San Joaquin Valley and the high desert were recognized. Although occasionally epidemic, coccidioidomycosis has principally been an endemic disease in certain California counties, with a background incidence of about 450 cases reported per year. In the early 1990s, however, there was a major resurgence of the disease in California that has led to a reexamination of public health control strategies.

Coccidioides immitis is a dimorphic fungus that grows as a mold in the upper levels of soil (saprobic phase) and as spore in its tissue (parasitic) phase. Ideal conditions for growth are a semiarid climate with a short, intense rainy season. Under favorable conditions, mycelia will grow and form arthroconidia at their distal tips; these arthroconidia will break off from the mycelia and become airborne with the slightest disturbance. Humans and other vertebrate hosts are exposed to *C immitis* by inhaling airborne arthroconidia, which expand to form characteristic spherules in the lungs at body temperature. These spherules cleave to form endospores that are released when the spherule bursts and, in turn, mature into new spherules. Immune response is cell-mediated, and investigators are gaining insight into which antigens are immunogenic. Symptomatic infection occurs in 40% of patients, with the principal symptoms being cough, fever, and chest pain. In a notable number of patients with primary infection, erythema nodosum will appear on the lower extremities, heralding the immunologic control of the infection; early investigators called this symptom complex "valley fever." The risk of dissemination is about 2% overall, but is increased for African Americans, Filipinos, Native Americans, pregnant women, elderly patients, and patients who are immunosuppressed. Principal complications are osteomyelitis, arthritis, and meningitis, all of which are difficult and expensive to treat.

The risk factors for acquiring coccidioidomycosis are exposure to dust during dry and windy conditions or because of the disruption of soil (for example, from construction) and exposure to soil (during archaeologic digs, for instance). Infection is common in residents of endemic areas. In studies of Native American children living in an endemic area of Arizona, the prevalence of infection was 9% among children younger than 5 years and 47% among 5- to 14-year-olds. As a result of seminal studies of coccidioidomycosis among Army Air Corps trainees in the San Joaquin Valley during World War II, one investigator observed that "practically every long-time resident of Phoenix, Arizona, Bakersfield, California, or El Paso, Texas, will have had his personal bout with *Coccidioides*."

The recent epidemiology of coccidioidomycosis in California is characterized by three interlinked epidemics. The first is the pronounced statewide increase in the number of reported cases that occurred between 1991 and 1995. During this five-year period, 14,086 cases of coccidioidomycosis were reported to the California Department of Health Services, with a peak of 4,517 cases in 1992. Of these cases, 8,931 (63%) were reported from Kern County. Only in 1996 has the incidence begun to approximate that of the pre-epidemic period, with 176 cases reported through week 10. This outbreak was probably the result of many factors, but two, the immigration of a nonimmune population to endemic areas and climatic conditions that were favorable to a multiyear bloom of *C immitis*, were probably the most important.

The second outbreak was one that occurred in Ventura County and was directly linked to dust clouds that em-

anated from landslides in the Santa Susanna Mountains caused by the Northridge earthquake in January 1994. In all, 170 cases were reported in a seven-week period following the earthquake. This outbreak is unusual in that Ventura County is not typically considered a hyperendemic area of coccidioidomycosis, although the Santa Susanna Mountains are part of the range that demarcates the southern range of the San Joaquin Valley. The climatic and soil factors that led to the general outbreak of coccidioidomycosis centered in Kern County also may have led to a similar bloom of *C immitis* on the southern edge of the Tehachapi range.

The third outbreak, which is intimately intertwined with the first, has occurred among patients with human immunodeficiency virus (HIV) infection in California. Coccidioidomycosis in the presence of HIV infection became a defining illness for the acquired immunodeficiency syndrome (AIDS) in the Centers for Disease Control's 1987 revision of the AIDS case definition. From 1987 to August 31, 1995, 317 cases of coccidioidomycosis had been reported among AIDS patients in California; in 158 (50%) of these, coccidioidomycosis was the first AIDS-defining opportunistic infection. Although accounting for only 0.3% of all AIDS-defining illnesses in California during this period, coccidioidomycosis accounted for 3.5% of new AIDS diagnoses in Kern County, 2.9% in Tulare County, and 2.2% in San Luis Obispo County. Interestingly, AIDS patients who had coccidioidomycosis as an AIDS-defining diagnosis were significantly more likely to be injection-drug users (18%) than those who had other AIDS-defining diagnoses (9%; $P = .006$).

The prevention of coccidioidomycosis is difficult, and efforts in the past have focused on preventing infection among short-term residents, such as military trainees, in endemic areas. In work with the Army Air Corps in World War II, one investigator focused on dust control—limiting construction during peak months, planting lawns, and paving roads and airstrips—to decrease the risk of infection. In one study, the attack rate among susceptible persons was 0.65% among recruits at Minter Field in Kern County, where these measures were employed, compared with 10% among German prisoners of war in a detention facility adjacent to Minter Field where these measures were not employed during the same 70-day period. Although other types of environmental controls have been discussed, such as the widespread application of fungicides or the use of respirators for construction workers, the ubiquity of the organism in its natural environment makes these measures and our traditional strategy of dust control less than adequate for controlling long-term exposure to the disease.

If we are unable to control long-term exposure to *C immitis*, the only remaining reasonable strategy to pursue is immunization. Attempts have been made to develop a vaccine for coccidioidomycosis, but these have been unsuccessful. Nevertheless, with the advancements in our understanding of the biology of the immune response to *C immitis* and with the general advancement in the techniques of molecular biology, coccidioidomycosis would seem a logical target for vaccine development. Unfortunately, given a commercial market limited to endemic areas, it is unlikely that vaccine manufacturers would embrace development.

Coccidioidomycosis has long been and continues to be a preventive medicine problem for the armed forces, however, and the Army, Navy, Marines, and Air Force still deploy large numbers of personnel to endemic areas. Perhaps the time is right for a new public-private partnership to be forged among commercial biotechnology firms, the Department of Defense, and the Public Health Service to exploit the new molecular biology and to focus an intensive research effort on a vaccine to prevent this important infection.

GEORGE W. RUTHERFORD, MD
MARK F. BARRETT
Berkeley, California

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Occupational Lead Exposure and Management

MANY ADVERSE HEALTH effects of lead exposure are recognized, including cardiovascular, reproductive, neurotoxic, metabolic, and hematologic abnormalities. As researchers have developed more sensitive indicators of outcomes, no clear threshold for lead's toxic effects has been found. To establish a practical objective for controlling the problem of occupational lead exposure, *Healthy People 2000* proposes the elimination of "exposures which result in workers having blood lead concentrations greater than 25 μg per dl [1.21 μmol per liter] of whole blood." The accomplishment of this goal is supported by two national lead standards established by the Occupational Health and Safety Administration (OSHA)—one for general industry (1979) and a newer one for construction work (1993). These standards require workplace monitoring by employers and establish medical monitoring for exposed employees. Public health agencies, however, do not routinely receive information to assess the actual exposures; instead, they do surveillance primarily through the reporting of blood levels by laboratories under mandatory state lead surveillance programs.

There are now 23 state lead registries that report blood levels to the Adult Blood Lead Epidemiology and Surveillance Program at the Centers for Disease Control and Prevention. Data from 1994 indicate that there are 12,137

adults with blood lead levels of 1.21 μmol per liter (25 μg per dl) or higher, and that extrapolates to about 19,000 cases nationwide. Research has shown that about 95% of cases of adult lead intoxication are occupational in origin. Given the recent implementation of the construction industry standard, data from the Occupational Lead Poisoning Prevention Program (OLPPP) at the California Department of Health Services begin to define the contribution of construction work to the overall lead problem. In 1993, the California OLPPP received reports on 1,163 workers with elevated lead levels (≥1.21 μmol per liter), with 161 (11%) from the construction industry. By comparison, 32% of reports are from storage battery manufacturers, 13% from smelting industries, and 7% from automotive radiator repair shops. The 1994 data showed 1,332 cases of elevated levels, with 106 (8%) from construction industries.

These surveillance data indicate that occupational lead exposure and poisoning remain a substantial problem as we approach the millennium. This point is underscored by the recognition of widespread noncompliance with the OSHA standard's requirements for blood testing of lead workers. For example, only 10 of 405 wrecking and demolition companies and 43 of 4,768 painting contractors in California reported blood lead levels in 1994.

Although there is good reason to think that the nation will not meet the *Healthy People 2000* objective to eliminate notable lead exposures, overall lead levels appear to be falling in the United States. Results from the Third National Health and Nutrition Examination Survey (NHANES III) (1988 through 1991) showed a geometric mean blood lead level for all ages to be 0.14 μmol per liter (2.8 μg per dl), which is down from 0.62 μmol per liter (12.8 μg per dl) in the NHANES II (1976 through 1980.) The declines were relatively consistent across all age categories. Nevertheless, in the NHANES III, 0.5% of adults aged 20 to 49 years had blood lead levels of 1.21 μmol per liter or higher, as did 0.3% of adults aged 50 to 69 years. Most of these adult elevations can be attributed to occupational exposure.

Various methods have been proposed to improve the control of occupational lead poisoning. Efforts to develop lead registries in states that do not have them and to standardize the practices among registries would allow for better surveillance and, an important element, case recognition. More personnel available to investigate reported cases would, in all likelihood, lead to the recognition of cases among co-workers and improved exposure control. Placing broader requirements on employers for blood lead medical surveillance has also been advocated.

A different approach to the problem is true exposure surveillance (or hazard surveillance). In this method, a list of lead-using industries would be established for the purpose of tracking the uses of this toxic agent and better determining the groups at risk. A pilot project of this type has been implemented with the automotive radiator industry in Los Angeles and San Bernardino counties, California. As a result of efforts to systematically identify the companies, to work with them to develop on-site lead poisoning prevention programs, and to maintain regular contact, the percentage of employees in medical surveillance went from 9% to 95%.

Apart from enhanced medical and hazard surveillance, another way to advance towards the *Healthy People 2000* goal is to eliminate or reduce the uses of lead. Product substitution or elimination is a key principle in occupational and environmental health. It has been used successfully in US lead policy by mandating greatly reduced use in gasoline and paint, and this can be credited for most of the decreases in lead levels found in the NHANES III. Proponents of this approach have advocated high excise fees on lead use in industry and increased research into substitute materials. California has established a fee on some of its lead products industries, but the fee is set primarily to finance public health efforts, not as a regulatory deterrent to lead use.

Practitioners in different settings are confronting the issue of how to provide the best medical care for an adult with an elevated lead level. Although many such cases are identified through surveillance by occupational medicine practitioners, a substantial number are discovered by other primary care professionals through good history taking, patient concerns, or symptoms. Confusion has occurred over the appropriate treatment protocol for adults, with some adults inappropriately receiving chelation therapy under guidelines intended for children. This misconception has perhaps been aggravated by the fact that some laboratories have sent out recommendations for chelation based on blood levels without considering the age of the patient.

As a result of inappropriate treatment and the use of chelating agents, management guidelines have been developed and are available from the California OLPPP—(510) 540-3448. The treatment of adults with chelating agents is based primarily on symptoms and is generally not indicated without symptoms. This is in contrast to child lead poisoning in which chelation is recommended in children with blood lead levels of 2.17 μmol per liter (45 μg per dl) or higher. Workers with blood lead levels between 0.48 and 1.16 μmol per liter (10 and 24 μg per dl) should have exposures identified and minimized. For adults with levels of 1.21 to 2.36 μmol per liter (25 to 49 μg per dl), there should be regular monitoring of blood lead and zinc protoporphyrin levels and the removal from exposure if symptomatic. Workers with blood lead levels above 2.40 μmol per liter (50 μg per dl) require removal from the workplace lead exposure in accordance with the OSHA standards, a complete medical evaluation, and ongoing monitoring with blood lead and zinc protoporphyrin levels. Practitioners should refer to appropriate federal or state lead standards for complete requirements of regulatory programs.

JAMES P. SEWARD MD, MPP
Berkeley, California

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Human Babesiosis and Ehrlichioses—Emerging Tick-Borne Diseases

LYME DISEASE was the emerging tick-borne infectious disease on the West Coast in the 1980s. Now, however, the diseases babesiosis and ehrlichiosis must also be considered in patients who are febrile and have a history of tick exposure.

Babesiosis is a malaria-like illness caused by a species of *Babesia*, an intraerythrocytic parasite. Fever, chills, headache, and hemolytic anemia are common, and diagnosis is made by finding ring-shaped intraerythrocytic parasites on blood smears. *Babesia microti* has been the primary strain causing human disease in the northeastern United States. Since 1991, however, five patients in the West—4 in California and 1 in Washington State—have been diagnosed with a *Babesia*-like organism designated WA1 (named for the first isolate in Washington State). Serum specimens from four of these five patients reacted to WA1 but not to *B microti*. All the California patients had a previous splenectomy, and one died of fulminant babesiosis, but the Washington patient was normosplenic and immunocompetent. From limited serosurveys, subclinical infection also occurs. The treatment of choice for disease with this new *Babesia*-like parasite has not yet been established, but patients have recovered after treatment with quinine and clindamycin. In the northeastern United States, *B microti* is transmitted by *Ixodes scapularis* ticks; the vector(s) for WA1 have not yet been identified.

Human ehrlichiosis is caused by two different species of *Ehrlichia*, which are obligate intracellular bacteria similar to rickettsiae. Human monocytic ehrlichiosis is caused by *Ehrlichia chaffeensis*, which invades mononuclear phagocytes, and human granulocytic ehrlichiosis is caused by a newly identified *Ehrlichia* species that is closely related to *Ehrlichia equi* and invades neutrophils. Exposure to *Ehrlichia* species may result in anywhere from asymptomatic infection to severe disease, the latter occurring particularly in older persons. Presenting signs and symptoms of ehrlichiosis due to either species are generally nonspecific: fever, chills, malaise, headache, muscle aches, and nausea. Blood tests commonly reveal elevated liver enzyme levels, leukopenia, and thrombocytopenia.

Since human monocytic ehrlichiosis was first described in 1987, more than 300 cases have been diagnosed, mostly in southern states. Human granulocytic ehrlichiosis, on the other hand, was first reported in 1994 in patients from Minnesota and Wisconsin and has since been identified in several northeastern states. In northern California, both human monocytic and granulocytic ehrlichioses are now diagnosed: in 1994 an elderly man was admitted to a hospital with a severe febrile illness due to human monocytic ehrlichiosis who had a greater than fourfold rise in levels of antibody to *E chaffeensis*. In 1995 human granulocytic ehrlichiosis was diagnosed by blood smear, polymerase chain reaction, and subsequently serologic tests in two adults, both of whom recovered with the administration of doxycycline. Both types of ehrlichioses can be treated effectively with doxycycline or tetracycline. The three California patients had not traveled out of their county in the three months before their illnesses began; two recalled removing a tick from themselves three weeks before their symptoms began. Whereas tick vectors for *E chaffeensis* in the southern states include *Amblyomia americanum* and *Dermacentor variabilis* and vectors for the human granulocytic ehrlichiosis agent in the Northeast include *I scapularis*, the tick vectors for *Ehrlichia* species in California have not yet been established.

There are measures the public can take to reduce the risk of tick-borne diseases: when spending time outdoors in tick-infested areas, wear long-sleeved shirts, long pants, and socks, tucking shirts into pants and pants into socks; wear light-colored clothing to facilitate seeing ticks; use tick-repellent products; check self and children carefully for ticks; and remove any attached tick by grasping it with tweezers as close as possible to the point of attachment and pulling gently away from the skin. On the West Coast, prophylactic treatment of persons bitten by ticks is not recommended currently.

DUC J. VUGIA, MD, MPH
VICKI L. KRAMER, PhD
Berkeley, California

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Directly Observed Therapy for Tuberculosis

FROM 1985 TO 1992, there was an increase in the number of active tuberculosis (TB) cases, from 22,000 to 26,673, reversing a downward trend of three decades. This resurgence in TB in the United States was due to multiple fac-

tors, including the human immunodeficiency virus (HIV) epidemic, homelessness, immigration, and treatment failures (often due to noncompliance). Noncompliance with the drug regimen and improper treatment prescriptions lead to multiple drug–resistant tuberculosis. Multidrug-resistant TB, defined as resistance to both isoniazid and rifampin, poses a substantial public health risk. An estimated 3.5% of cases of TB are resistant to these drugs, with higher rates in multidrug-resistant risk groups, which include HIV-positive persons, immigrants from drug-resistant areas, contacts of persons with multidrug-resistant TB, and persons previously treated for TB. Compliance with treatment is complicated by the length of treatment required, multiple medication regimens, side effects, and the setting in which TB is found—poverty, homelessness, and drug abuse. Previous techniques to assess compliance, such as verbal reporting, pill counts, and clinical progress, have failed.

Solutions to compliance problems include shorter regimens given by directly observed therapy. During directly observed therapy, health care workers directly observe the ingestion of the medications the entire course of treatment, which varies from 6 to 18 months, with medications given from two to five times per week. Directly observed therapy has been widely studied in Hong Kong, East Africa, and India and has been shown to be successful and practical in various environments, both urban and rural. Studies in the United States evaluating directly observed therapy have also shown substantial reductions in the incidence of directly observed therapy and in the frequency of primary TB drug resistance, acquired drug resistance, and TB relapse. In Baltimore, Maryland, Tarrant County, Texas, and New York City, successful results have been achieved in these US communities where directly observed therapy has been implemented. These studies have contributed to early reports of an improvement in the rates from 1993 to 1995.

Although some directly observed therapy programs require the patients to present themselves to the health care facility at the required interval, directly observed therapy is also conducted in patients' homes or shelters. Temporary housing has been provided by public health departments during the course of directly observed therapy to provide a stable environment during drug treatment. Directly observed therapy given in a patient's own environment is especially useful where transportation problems, language barriers, and social barriers would affect compliance with scheduled appointments at a health care facility.

Directly observed therapy is strongly advocated and supported as a community standard for both the public and private sectors by the National Jewish Hospital and other agencies with expert knowledge in treating TB, but its universal use is still an active topic of debate. Although cost factors should be taken into account and some patients can be expected to be fully compliant, directly observed therapy should be considered for all patients with active TB and used at a minimum for all who have multidrug-resistant TB and for any whose compliance might be in question.

The California TB Controllers Association has identified the following as risk factors for nonadherence to TB treatment regimens: history of alcohol or drug abuse, history of correctional incarceration, homelessness, major psychiatric or memory cognitive disorder, history of adverse reactions to previous TB treatment, poor acceptance of TB diagnosis, inability to manage self-care, and adolescence. Other indicators of possible noncompliance include slow clinical improvement or sputum conversion or clinical deterioration while receiving therapy. Children of persons in these groups are also likely to receive incomplete treatment without directly observed therapy. Medical community and public support for aggressive surveillance and directly observed therapy is essential, even if rates of TB continue to decrease, to avoid a resurgence of the disease.

ELIZABETH MANNINO, MD, MPH
LINDA HILL, MD, MPH
San Diego, California

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Multidrug-Resistant Tuberculosis—How Far Are We From New York City?

MULTIDRUG-RESISTANT tuberculosis, defined as tuberculosis (TB) that is resistant to both isoniazid and rifampin, has dreadful public health consequences. Multidrug-resistant TB organisms are not susceptible to the two most active antituberculosis drugs. Treatment generally requires more toxic and less effective medications given for longer duration (as long as 24 months after culture conversion to negative). The success rate of treatment is far inferior to that of drug-sensitive TB. The efficacy of currently recommended preventive regimens for multidrug-resistant TB is unknown. Before the 1990s, outbreaks of multidrug-resistant TB in the United States were scattered and sporadic. The steady decline in the number of newly reported cases of TB reversed after 1985. Soon thereafter came reports of multidrug-resistant TB outbreaks, many of which occurred in New York City. These more recent outbreaks were characterized by transmission to large numbers of people, including health care workers; rapid progression from infection to disease; and high mortality, attributed to the fact that many patients were also infected with the human immunodeficiency virus (HIV). We must begin to question how close we in

the West might be to the scenarios described in New York City and what can be done to prevent similar public health disasters here.

In 1994 the Centers for Disease Control and Prevention published findings of a national survey of drug-resistant TB in the United States. During the first three months of 1991, a total of 3,256 cases were identified that were tested to both isoniazid and rifampin, and 114 (3.5%) of these were resistant to both drugs. Of 64 cities with populations over 250,000, 7 reported multidrug-resistant TB cases, and although the highest resistance rate was in New York City (13.9%), three California cities—Oakland, Sacramento, and Los Angeles—were included. Los Angeles is the most populous California city on the list, and the county of Los Angeles is even larger, containing more than 9 million people (more than 42 entire states). Nevertheless, of 1,622 new TB cases reported from Los Angeles County (excluding Pasadena and Long Beach) in 1995, only 20 (1.2%) had multidrug-resistant TB (TB Control, Los Angeles County, provisional data), and the resistance rate continues to be far below that of New York City. The factors that are thought to have contributed to the development of multidrug-resistant TB and subsequent outbreaks are all present in Los Angeles County, including homelessness, immigration, substance abuse, nonadherence to drug regimens, and an HIV epidemic. Why isn't multidrug-resistant TB more common, and what can we do to prevent future outbreaks?

Since 1985, the Los Angeles County Health Department has used Rifamate (Marion Merrell Dow), a fixed-dose combination antituberculosis medication containing both isoniazid and rifampin. The use of this formulation may partly explain the low rates of multidrug-resistant TB in this county because it prevents patients from taking either drug alone, thus decreasing the risk of drug resistance developing from unintended monotherapy. The use of Rifater (Marion Merrell Dow), a fixed-dose preparation containing isoniazid, rifampin, and pyrazinamide, should also be considered when starting patients on empiric treatment pending susceptibility results.

Drug resistance is also prevented by interventions such as directly observed therapy that increases patient adherence to and completion of treatment. Incentives may do the same. In Los Angeles County, the percentage of homeless patients in the Skid Row area completing treatment was 53% in 1987. But by 1994, about five years after the creation of a food-and-housing incentive program, this had increased to 96%.

Finally, rapid and accurate clinical diagnosis shortens the duration of infectiousness by ensuring prompt treatment with appropriate medications. This is especially important in persons with the acquired immunodeficiency syndrome, whose symptoms may be attributed to *Mycobacterium avium* complex when *Mycobacterium tuberculosis* is the real culprit. Obtaining specimens for culture confirmation and susceptibility testing, preferably before starting an antimycobacterial drug regimen, is critical in this population, as is ruling out active TB before starting preventive therapy.

Public health interventions must be aggressively applied because the factors for multidrug-resistant TB outbreaks are all present in Los Angeles, and New York City is much closer than we think.

ANNETTE NITTA, MD
Los Angeles, California

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Smoking Cessation—New Challenge and Opportunities

THE NEED FOR and means of assistance with smoking cessation have seldom been greater than in 1996. Increasingly, both the adverse effects of smoking and the availability of effective means of assisting smoking cessation are clear. Increases in both the strength and range of smoking-related risks have been noted since the 1960s. Smoking-cessation behavioral and pharmacotherapies are rapidly increasing in availability and ease of use.

Pharmacotherapies for stopping smoking now include nicotine (polacrilex) gum, patches, and nasal spray; the first two have recently become available over the counter in drugstores. Antidepressants are increasingly being investigated as an aid to stopping smoking, with the use of bupropion hydrochloride showing the most promise to date.

The availability of smoking-cessation aids is dramatically increasing. Inexpensive or free outbound phone counseling such as the multilingual California Smokers' Helpline (1-800-7NO-BUTTs) or insurer or private phone services are widely, promptly, and conveniently available. Federal (Agency for Health Care Policy and Research) guidelines on smoking cessation assistance are free by calling 1-800-358-9295.

Highly concentrated smoking-related risks exist in continuing smokers and are amenable to intervention in physicians' offices. The "Ask, Advise, Assist, and Arrange" model of smoking-cessation assistance is recommended. Clinicians are encouraged to ask about their patients' smoking status. Physicians should advise smokers of smoking's risks and the benefits of stopping. Assisting patients by providing them pamphlets, nicotine replacement, or referrals to phone, class, or other smoking-cessation resources increases quit rates. Arrangements for follow-up are important to support patients' smoking-cessation efforts.

BRUCE N. LEISTIKOW, MD, MS
Davis, California

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Naltrexone Hydrochloride Use in the Treatment of Alcoholism

ALCOHOLISM IS a primary chronic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. The disease is often progressive and fatal. It is characterized by impaired control over drinking, preoccupation with the drug alcohol, the use of alcohol despite adverse consequences, and distortions in thinking, mostly denial. It is one of the most pervasive medical and social problems of our time. Not surprisingly, the treatment of alcoholism is also one of the most elusive, not only of this generation but since civilizations have been crushing grapes to make wine.

To date, the treatment of alcoholism has largely been characterized by detoxification and referral to various rehabilitation programs—12-step groups, recovery homes, church, and psychotherapy. Disulfiram (Antabuse), which blocks the metabolism of alcohol, produces a possibly toxic reaction with noxious effects that include nausea, vomiting, headache, and facial flushing. Although it has been available for many years, its efficacy has been shown only in patients who are willing to take the medication daily and are participating in a rehabilitation program.

The development of naltrexone hydrochloride as a pharmacologic adjunct to the treatment of alcoholism was based initially on studies using animals that looked at excessive alcohol consumption. It was found that alcohol-preferring strains of mice and rats have increased basal β-endorphin levels in the pituitary gland and in some brain areas relative to alcohol-nonpreferring rats. When alcohol-preferring rats were given naltrexone hydrochloride, a pure opioid antagonist, alcohol consumption decreased. In humans, nonalcoholic persons with a strong family history of alcoholism (high risk) were compared with nonalcoholic persons with no family history of alcoholism (low risk). Baseline plasma β-endorphin levels were lower in the high-risk group, and a small dose of alcohol caused a substantially greater increase in plasma β-endorphin levels than in those of the low-risk group. Based on these and other studies, the endogenous opioid hypothesis was formulated that proposes that the ingestion of alcohol stimulates the release of endogenous opioids that increase some of the rewarding effects of alcohol. This is not to say that endorphins are the only neurotransmitter involved in the behavior associated with alcohol consumption; serotonin and dopamine have also been implicated, and clearly there are multiple mechanisms that need further study.

What has been shown in other studies is that naltrexone hydrochloride use does seem to reduce craving, the relapse rate, and the "high" associated with alcohol consumption when combined with some form of psychological or social therapy. Studies were conducted using patients from the Philadelphia (Pennsylvania) Veterans Affairs Medical Center who had 20 years or more of heavy alcohol use; met 5 of 9 criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised, for alcohol dependence; and did not have a major psychiatric illness. During the 12-week period when patients received naltrexone hydrochloride, 50 mg per day, versus placebo, the placebo-treated group met criteria for relapse in 54% of cases, but the drug-treated group met criteria in only 23% of cases. Relapse criteria included drinking five or more days within a week, five or more drinks per drinking episode, or coming to the clinic with a blood alcohol level of higher than 22 nmol per liter (100 mg per dl).

Clearly it could be argued that the accepted standard of care or the treatment goal in alcoholic patients is total abstinence. Naltrexone use seems to reduce the risk of relapse but does not prevent a person with alcoholism from picking up the first drink. Thus, naltrexone may be most effective in patients with a higher risk for relapse—that is, patients with greater somatic symptoms and higher levels of alcohol craving, when accompanied by some form of behavioral or social therapy.

STEVEN R. EY, MD
Corona Del Mar, California

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Alerts, Notices, and Case Reports

Spontaneous Group B Streptococcal Meningitis in a Patient With Cirrhosis

BRUCE Y. TUNG, MD
KRIS V. KOWDLEY, MD
Seattle, Washington

GROUP B STREPTOCOCCI (*Streptococcus agalactiae*) are the leading cause of sepsis and meningitis in neonates.[1,2] The importance of invasive group B streptococcal infections in adults has been increasingly recognized.[3,4] The most common sites of adult infection are skin or soft tissue, blood (bacteremia) with no identifiable source, urinary tract, and lungs (pneumonia).[5] Group B streptococcal meningitis in adults is relatively rare and often associated with underlying medical conditions such as diabetes mellitus, cancer, renal failure, cardiac disease, steroid use, and collagen vascular disease.[6,7] To our knowledge, there has been no previous case of group B streptococcal meningitis reported in an adult with advanced liver disease.

We present the case of a patient with cirrhosis due to chronic hepatitis C infection in whom spontaneous group B streptococcal meningitis developed. This case shows the susceptibility of cirrhotic patients to unusual infections and the ease with which bacterial meningitis might be mistaken for hepatic encephalopathy in a patient with advanced liver disease.

Report of a Case

The patient, a 52-year-old man, was brought to the emergency department after being found confused and agitated. He had a known history of biopsy-proved cirrhosis due to chronic hepatitis C infection and previous admissions for hepatic encephalopathy. The patient had been well until three days before admission, when he had right upper quadrant pain, diarrhea, and vomiting. Increasing shortness of breath and increasing lethargy subsequently developed. The morning of admission, the patient was found agitated and unresponsive.

On arrival at the emergency department, the patient was confused, agitated, and jaundiced. He was afebrile but was noted to have tachycardia, hypertension, and tachypnea. Brudzinski's and Kernig's signs were absent. His lungs were clear, and cardiac examination revealed a grade II/VI systolic murmur at the left lower sternal border. Abdominal examination revealed no distension or obvious ascites. There was no abdominal tenderness and no hepatomegaly. The spleen tip was palpable in the left upper quadrant. On mental status examination, the patient was awake, but wildly agitated and combative. He moved all extremities spontaneously and had symmetric deep tendon reflexes. Rectal examination showed Hemoccult-positive brown stool.

Laboratory values included a leukocyte count of 16.7 $\times 10^9$ cells per liter (16,700 cells per mm^3), of which 0.73 (73%) were neutrophils and 0.20 (20%) were lymphocytes. The hematocrit was 0.32, and the platelet count was 51 $\times 10^9$ per liter (51,000 per mm^3). A serum sodium level was 134 mmol per liter; potassium, 4.5 mmol per liter; chloride, 104 mmol per liter; bicarbonate, 16 mmol per liter; blood urea nitrogen, 18.0 mmol per liter (51 mg per dl); and creatinine, 150 μmol per liter (1.7 mg per dl). The serum bilirubin level was 128 μmol per liter (7.5 mg per dl); serum aspartate aminotransferase, 62 U per liter (normal, 10 to 29); and serum alanine aminotransferase, 40 U per liter (normal, 6 to 27). A prothrombin time was 19 seconds (normal, 11 to 13.6), and a venous ammonia level was 42 μmol per liter (71 μg per dl; normal, 0 to 35 μmol per liter). Arterial blood gas values with the patient receiving supplemental oxygen at 4 liters per minute showed a pH of 7.39, a P_{CO_2} of 29 mm of mercury, and a P_{O_2} of 94 mm of mercury.

Orogastric aspirate revealed Gastroccult-positive dark material without gross blood. The patient's altered mental state was initially ascribed to hepatic encephalopathy exacerbated by gastrointestinal bleeding, and a regimen of lactulose enemas was started. The patient was agitated out of proportion to that usually seen with hepatic encephalopathy, however, and with concomitant leukocytosis, the diagnosis of bacterial meningitis was considered. He was intubated for airway protection and given ceftriaxone sodium, 1 gram intravenously. A chest radiograph revealed bilateral upper lobe infiltrates, and a noncontrast computed tomographic scan of the head was unremarkable. A lumbar puncture was done and revealed 50 $\times 10^6$ erythrocytes per liter (5,000 per mm^3) and 36.75 $\times 10^6$ leukocytes per liter (3,675 per mm^3), of which 0.88 (88%) were neutrophils and 0.12 (12%) were mononuclear cells. A cerebrospinal fluid (CSF) glucose level was 0.61 μmol per liter (11 mg per dl), and the CSF protein value was 3.4 grams per liter (343 mg per dl).

Cultures of CSF and blood grew group B streptococci sensitive to penicillin. The patient's regimen was promptly switched to intravenous penicillin G, 24 million units per day, but multisystem organ failure rapidly developed, with acute renal failure, hepatic failure, and the adult respiratory distress syndrome. On the ninth hospital day, increasing pulmonary infiltrates developed, and he had worsening oxygenation and progressive hepatic dysfunction. Despite broadening of the patient's antibiotic regimen to cover nosocomial pneumonia, he died on the 15th hospital day. No further cultures grew out group B streptococci.

(Tung BY, Kowdley KV: Spontaneous group B streptococcal meningitis in a patient with cirrhosis. West J Med 1996; 165:229–230)

From the Division of Gastroenterology, Department of Medicine, University of Washington School of Medicine, Seattle.

Reprint requests to Kris V. Kowdley, MD, University of Washington School of Medicine, Mailbox 356424, Seattle, WA 98195.

Discussion

Group B streptococci are the leading cause of neonatal sepsis and meningitis, with an estimated incidence of 1.8 per 1,000 live births.[2] In adults, the incidence of invasive group B streptococcal infections appears to be increasing. Population-based studies in metropolitan Atlanta, Georgia, have shown an incidence of 4.4 cases per 100,000 nonpregnant adults in 1993, nearly double that of the same population studied retrospectively from six years earlier.[3,5] Older persons are at a substantially increased risk of invasive group B streptococcal infection, with an incidence in those 60 years of age or older of 18 cases per 100,000.[5] A recent multivariate analysis revealed that patients with cirrhosis are also at a significantly increased risk (odds ratio, 9.7) for community-acquired invasive group B streptococcal infection.[4] Other conditions that have been shown to predispose to community-acquired invasive group B streptococcal infection include diabetes mellitus, stroke, breast cancer, decubitus ulcer, and neurogenic bladder.[4]

Of all adult cases of invasive group B streptococcal infection, meningitis accounts for only 3% to 4%.[2,4-6] In all, 52 cases of group B streptococcal meningitis in adults have been reported in the English-language literature from 1966 to the present. A recent review of these cases showed that the average age of patients affected is 54 years, although there appears to be a bimodal distribution with peaks in the third and in the eighth decades of life.[6] Comorbid conditions are associated with adult group B streptococcal meningitis in more than half the cases.[6,7] The precise immunologic mechanisms by which these conditions predispose to invasive group B streptococcal disease have not yet been elucidated. To date, no case of group B streptococcal meningitis has been reported in an adult patient with advanced liver disease.

Patients with chronic liver disease are more susceptible to bacterial infections because of reduced activity of the mononuclear phagocyte system,[8] as well as depressed opsonic activity of serum and ascites.[9] Dysfunction of macrophage Fcγ receptors has been demonstrated in patients with alcoholic cirrhosis and may predispose to bacterial infection.[10] Although complement levels may be normal in chronic liver disease, there are deficiencies in complement activation, opsonization, and neutrophil chemotaxis.[11] Alterations in intestinal flora, gastrointestinal hemorrhage, and frequent invasive diagnostic testing may also play a role in susceptibility to bacterial infections. In a recent prospective study of 170 patients with cirrhosis requiring admission to a hospital, bacterial infections developed in 47%, although no cases of meningitis were found.[12]

The current case illustrates the fact that in a patient with cirrhosis, bacterial meningitis may be easily mistaken for hepatic encephalopathy. This patient was initially thought to have hepatic encephalopathy on the basis of mental status changes associated with known cirrhosis, evidence of gastrointestinal bleeding, and an elevated serum ammonia level. Given his agitation out of proportion to that usually seen with hepatic encephalopathy, however, alternative diagnoses such as bacterial meningitis were considered, and a lumbar puncture was done. The precise source of this patient's bacteremia is unknown. Pneumonia accounts for 12% of cases of group B streptococcal infection,[4] but this organism was not isolated from the patient's sputum. Group B streptococcal peritonitis has been described, but was not suggested by this patient's clinical presentation. In all cases of invasive group B streptococcal infections in adults, the most common finding is bacteremia without an evident source.[4,5]

Despite prompt empiric treatment with antibiotics and appropriate narrowing of the therapeutic regimen to penicillin G when CSF and blood cultures grew out *S agalactiae*, multisystem organ failure developed, and this patient died. This clinical course is consistent with mortality data from the 52 previously reported cases of adult group B streptococcal meningitis. In those cases, the overall mortality was 27%. In patients with associated comorbidity, however, mortality was 45% compared with 0% in patients without associated illness.[5]

Vaccines for group B streptococci are currently being developed.[13] Although much attention has been focused on the application of these vaccines to perinatal care, the increasing incidence of invasive group B streptococcal disease in adults necessitates attention. Further study into the host mechanisms that predispose to group B streptococcal infection may point to subgroups of adults, such as those with cirrhosis, who might benefit from immunoprophylaxis.

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Lysinuric Protein Intolerance Presenting as Coma in a Middle-Aged Man

MEIR GARE, MD
MEIR SHALIT, MD
ALISA GUTMAN, MD
Jerusalem, Israel

LYSINURIC PROTEIN INTOLERANCE was first described in 1965 as "protein intolerance and defective transport of basic amino acids."[1] The highest incidence of the disease is in Finland (1 per 60,000 to 80,000 live births); sporadic cases have been described from many other places. The underlying defect has been shown to be the impaired transport of dibasic amino acids in the basolateral membranes of intestinal, hepatic, and renal tubular cells.[2–6] Unlike other defects of intestinal and renal aminoacid transport, such as cystinuria and Hartnup disease, lysinuric protein intolerance is associated with the failure to thrive, vomiting, and diarrhea in early childhood. The disease is characterized by protein aversion, hepatosplenomegaly, muscular weakness, osteoporosis, sparse hair, and a high prevalence of interstitial lung disease.[7,8] Recurring postprandial hyperammonemia has been shown to be due to a deficiency of ornithine in liver mitochondria.[5] In addition to elevated levels of ammonia, laboratory examination usually reveals elevated levels of lactate dehydrogenase (LDH), aspartate aminotransferase, alanine aminotransferase, aldolase, ferritin, and thyroid-binding globulin. In addition, mild leukopenia, anemia, or thrombocytopenia also occur.[6]

We present the case of a middle-aged man who was admitted to the emergency department in a state of coma as the presenting symptom of lysinuric protein intolerance.

Report of a Case

The patient, a 43-year-old Ashkenazy-Jewish man, was admitted as an emergency case after being found comatose in his car, which was parked by the roadside. The history, taken from his wife, revealed that for three days before admission the patient had diarrhea, weakness, and low-grade fever. From his medical history, the wife reported that as a young adult he had had two episodes of confusion, one of them attributed to cerebral malaria and the second one, which was accompanied by right hemiparesis, attributed to a left hemispheric cerebrovascular accident. Other medical problems included mild hypertension since the age of 20, for which he took sustained-release nifedipine, 10 mg twice a day. The family history revealed that his father, brother, and daughter had had hypertension since their early 20s.

(Gare M, Shalit M, Gutman A: Lysinuric protein intolerance presenting as coma in a middle-aged man. West J Med 1996; 165:231–233)

From the Department of Internal Medicine, Michael Reese Hospital, Chicago, Illinois (Dr Gare); the Division of Internal Medicine (Dr Shalit) and Department of Clinical Biochemistry (Dr Gutman), Hadassah University Hospital, Jerusalem, Israel.

Reprint requests to Meir Gare, MD, Dept of Internal Medicine, Michael Reese Hospital, 2929 S Ellis Ave, Chicago, IL 60616.

ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
LDH = lactate dehydrogenase

On physical examination, the patient was in a state of coma with spontaneous breathing and symmetric normal reflexes. No neck stiffness or papilledema was found, and a normal pupillary response was elicited. His temperature was 36.1°C (97°F), blood pressure was 170/100 mm of mercury, and he had a regular pulse rate of 92 per minute. The lungs were clear, and heart auscultation was within normal limits. Abdominal palpation showed moderate hepatosplenomegaly. Routine laboratory test values, including electrolytes, glucose, calcium, bilirubin, total protein, albumin, ceruloplasmin, and copper, were all within normal limits. The only abnormalities detected were a mildly elevated plasma ammonia level (150 μmol per liter [255 μg per dl]), a below-normal plasma urea level (0.8 mmol per liter), and an elevated LDH level (1,990 U per liter; normal, 300 to 620) and creatine kinase value (720 U per liter; normal, <110). Cultures of blood, cerebrospinal fluid (CSF), urine, and stool were negative for pathogens. Liver serologic tests, including hepatitis A, B, and C virus, were negative. An electroencephalogram showed severe irregularity and nonrhythmic activity, mainly diffuse slow delta and triphasic waves with no focal predominance, and it was interpreted as indicating severe meta- bolic encephalopathy. Brain computed tomography revealed diffuse cortical atrophy with no signs of a previous or recent cerebrovascular accident.

To confirm that the patient's coma was due to hyperammonemia, the CSF glutamine level was measured by an amino acid analyzer. The gross elevation of the CSF glutamine level to more than 2,700 nmol per ml (normal, <650) confirmed the initial diagnosis, but left the question of the cause of the hyperammonemia open. Closer inspection of the amino acid chromatogram revealed the virtual absence of arginine, ornithine, and lysine, all of which appear in substantial concentrations in normal CSF (20 to 40 nmol per ml). The almost complete absence of dibasic amino acids from the CSF prompted an analysis of plasma amino acids, which also showed reduced concentrations of the dibasic amino acids and elevations of glutamine and alanine expected in hyperammonemic states (Table 1). Levels of other plasma amino acids, including cystine, were within the normal range. The association of hyperammonemia with low plasma and CSF concentrations of dibasic amino acids raised the possibility that this was a case of lysinuric protein intolerance.

Further questioning of the patient revealed that as an infant, he had suffered from a failure to thrive and that since childhood he had been a strict vegetarian because of an aversion to meat. It was also noted that he was of short stature and had sparse reddish hair. The patient was treated with fluids, neomycin, and lactulose to reduce the

TABLE 1.—*Plasma and Cerebrospinal Fluid (CSF) Amino Acid Levels (nmol per ml) in a Patient With Lysinuric Protein Intolerance**

	Plasma		CSF	
Amino Acid	*Patient*	*Controls*	*Potient*	*Controls*
Ornithine	20	30 to 150	Trace	20 to 30
Lysine	60	120 to 140	Trace	35 to 45
Arginine	22	30 to 140	Trace	10 to 37
Citrulline	11	0 to 35	5.6	1.2 to 7.8
Glutamine	1,731	413 to 690	>2,700	500 to 650
Alanine	874	200 to 600	35.7	40 to 50

*Amino acids were measured on a Perkin Elmer-Pickering Amino Acid Analyzer by ninhydrin-based postcolumn derivatization.

ammonia load in the intestine. Within three days, he recovered from the coma, but amnesia of the acute event persisted. The patient was discharged with the recommendation to supplement his diet with 5 to 7 grams of citrulline per day, as recommended elsewhere.[9] Following his recovery from the acute event, the patient and his family refused further studies and were lost to follow-up.

Discussion

Syndromes of hyperammonemia and encephalopathy can be inherited or acquired[10] and include urea cycle enzyme deficiencies (for example, ornithine carbamoyltransferase deficiency), organic acidemias (such as propionic acidemia), and transport defects of urea cycle intermediates as lysinuric protein intolerance. Most of the acquired hyperammonemic and encephalopathic syndromes, such as Reye's syndrome and hepatic encephalopathy in patients with cirrhotic liver, are attributed to a failure of liver function. Normal liver function test results and the absence of signs of liver cirrhosis should alert a physician to the possibility of a congenital disorder as the cause of the syndrome, even in an adult.

Lysinuric protein intolerance is a rare cause of coma due to episodic hyperammonemia on ingesting protein or during catabolic states.[11] This disorder is usually diagnosed soon after weaning in children with failure to thrive, associated with vomiting and diarrhea. In a series of 19 patients, diagnosis was made in early childhood in 13 cases and at ages 10 to 14 in 5; only one patient was 22 years old at the time of diagnosis.[12] In our patient, all the clues for a correct diagnosis were present since childhood: a failure to thrive, an aversion to protein-containing foods, and later, episodes of cerebral dysfunction.

The reason for the failure to diagnose the patient's condition in childhood may be related to the fact that he was born in Hungary during the first decade after World War II and grew up as a recent immigrant in Israel at a time when "failure to thrive" was widespread and was ascribed to economic factors. A similar case was noted in a 36-year-old Finnish woman who was sent to a foster home in Sweden in 1942 at the age of 7 years. Once such a person is past childhood, there is little chance of a correct diagnosis being made, except during an attack of hyperammonemia-induced cerebral dysfunction.[13] From the history of our patient, we know of at least two such occasions where routine plasma ammonia determinations would have led to the proper diagnosis.

After the current hyperammonemic episode, the patient was amnesic concerning the events preceding the coma, and this seems also to have been the case in previous attacks, which may have been more numerous. The factor initiating the current attack was a catabolic state after several days of a febrile illness associated with gastroenteritis.

The clue to the diagnosis in this case came from amino acid chromatography of CSF. To the best of our knowledge, CSF amino acids have not previously been evaluated in this condition. The almost complete disappearance of arginine, lysine, and ornithine from CSF raises the possibility of a transport defect for dibasic amino acids at the blood-brain barrier, in addition to the known intestinal, renal, and hepatic defects. It is also possible that the reduced levels of one or more of these amino acids in the brain are responsible for the diffuse cortical atrophy found in the computed tomographic scan of the brain. Brain atrophy has been noted previously in two adult patients.[2]

Minor features noted in previous cases that were also present in our patient were hepatosplenomegaly and elevated levels of LDH. A feature that was never noted in previous cases is the elevated level of creatine kinase that was present in our patient. This patient his daughter, brother, and father all had hypertension since an early age. It is tempting to speculate that hypertension in this family is related to the low levels of arginine found in the patient's plasma. A recent article describes the case of an infant who could not synthesize L-arginine because of argininosuccinate lyase deficiency and who was hypertensive before arginine replacement. The infusion of arginine resulted in a reduction of the blood pressure, with a return to previous levels on the cessation of treatment.[14] In another article, arginine deficiency induced experimentally in rats caused a substantial elevation of the blood pressure.[15]

This report stresses the importance of considering urea cycle–related factors in adult patients admitted with unexplained coma. Observations on additional patients with reduced plasma arginine levels will be necessary to include hypoargininemia among risk factors for hypertension in young patients.

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Topics in Primary Care Medicine

Parkinson's Disease
Diagnosis and Treatment

DON C. NG, MD, *San Francisco, California*

Although Parkinson's disease is primarily a neurologic disorder, primary care physicians should be knowledgeable about the disease and its treatment because most patients will see their primary care physician first for their symptoms. Furthermore, in today's setting of managed care, primary care physicians will likely be called on even more to assume primary responsibility for the treatment of patients afflicted with Parkinson's disease; neurologists will likely play the role of consultants who see a patient only periodically and offer recommendations and advice for the primary care physicians to implement.

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The prevalence of Parkinson's disease in community-based studies is 128 to 187 per 100,000, with an annual incidence of 20 per 100,000 in the United States.[1] As many as 1.5 million Americans are affected, and 1% of the population older than 60 years may be affected.[2] Men may be more frequently affected than women, but most community-based studies from other countries worldwide do not show a gender preference.[1] The mean age of onset is in the mid-50s, with increasing incidence and prevalence thereafter; of note, 10% of all patients have recognizable symptoms before the age of 40 and 30% before age 50.[3] The cause is unknown; many causes have been proposed but not borne out by subsequent studies. A leading theory is that oxidative stress may be a contributing factor to the loss of melanized cells of the substantia nigra. The clinical importance of these oxidative mechanisms has yet to be proved.

Natural History

Parkinson's disease is usually slowly progressive over decades in both treated and untreated patients, but the rate of progression varies widely among individual patients, ranging from 2 to 30 years until severe disability or death. The tremor-dominant type of Parkinson's disease and an older age of onset may be associated with a faster rate of progression and a higher risk of cognitive failure developing.* Treatment with levodopa does seem to decrease the severity and to delay the onset of severe disability and related death, hence improving the quality of life. The use of levodopa has increased the mean duration of disease from about 10 to 14 years and reduced the mortality rate among Parkinson's patients. Before the development of levodopa therapy, mortality was three times higher for patients with Parkinson's disease than for the general population for the same age, sex, and race; for patients treated with levodopa, this ratio has been reduced to 1.2 to 1.[3,4]

Diagnosis

The diagnosis of Parkinson's disease is entirely clinical and mostly one of exclusion because there are no diagnostic tests or studies for the disease. It is defined histologically as a loss of pigmented neurons mostly in the substantia nigra, along with characteristic eosinophilic cytoplasmic inclusions known as Lewy bodies. The pathologic neurochemical process is an insufficiency of striatal neurotransmitters, predominantly dopamine, which has to be reduced to 20% to 30% of normal before clinical manifestations occur. Early Parkinson's disease can be difficult for primary care physicians to diagnose because the early symptoms, sometimes referred to as the preclinical or subclinical phase, may precede the "clinical" onset—when clinical criteria are met—by a decade or two.[4] Early symptoms such as slowness, weakness, fatigue, loss of appetite, and sleep disturbances are nonspecific and can lead to a misdiagnosis of hypothyroidism or depression. Another common misdiagnosis is stroke because early symptoms are often unilateral.[5]

The cardinal symptoms of Parkinson's disease are resting tremor (classic pill-rolling type); muscular rigidity with "cogwheeling" resistance to passive movement; bradykinesia manifesting as decreased blinking, mask-like facies, and slowness of movement; postural instability manifesting as retropulsion; gait disturbance with a wide-based, shuffling gait and flexed posture; and a unilateral onset of symptoms with an asymmetric development of disease.[5,6] The diagnostic accuracy using

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From the Division of General Internal Medicine, University of California, San Francisco (UCSF), School of Medicine.

Reprint requests to Don C. Ng, MD, Division of General Internal Medicine, UCSF, 400 Parnassus Ave, A-405, San Francisco, CA 94143-0320; E-mail: don_ng@ucsfdgim.ucsf.edu.

ABBREVIATIONS USED IN TEXT

DATATOP = Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism
MAO = monoamine oxidase
MPTP = methylphenyltetrahydropyridine
MRI = magnetic resonance imaging

these criteria is poor in clinical practice; 20% to 30% of patients with clinical parkinsonism other than histologically verified Parkinson's disease are erroneously diagnosed during life.[6] Another criterion used is a good to excellent response to levodopa or a dopamine agonist. Exclusionary criteria include the absence of substantial changes on brain imaging other than mild diffuse cortical atrophy on computed tomography or magnetic resonance imaging (MRI) or mild periventricular disease on MRI; the absence of pyramidal and cerebellar signs; the absence of a history of drugs, toxic substances, or encephalitis that may cause parkinsonism; and the absence of features atypical for Parkinson's disease. The presence of substantial dementia or autonomic failure out of proportion to the degree of parkinsonism points to other neurodegenerative disorders, although the presence of either in a mild to moderate degree may still be consistent with Parkinson's disease.[6] One study assessed the accuracy of nine clinical features of patients diagnosed with Parkinson's disease by the postmortem histologic examination of brain tissue.[7] The results showed that the clinical criteria for Parkinson's disease had varying degrees of sensitivity and specificity. This may explain why there is no universally accepted set of clinical criteria for the diagnosis.

Attempting to learn and apply the differing sets of criteria proposed by various research groups for the diagnosis of Parkinson's disease would prove to be a daunting task and an unwieldy tool for primary care physicians. Many of the proposed criteria were put forth in an attempt to improve the accuracy of the diagnosis for research purposes. Thus, although more specific, the proposed criteria are less sensitive and exclude many patients with the disease. In a clinical setting, it may be better to be more sensitive and less specific so that more patients with true Parkinson's disease will have a better chance of being treated. A simple approach for primary care physicians is to remember the cardinal features of tremor, rigidity, bradykinesia, postural instability, and gait disturbances and think of the other features mentioned earlier as "supporting evidence," namely, asymmetry, a good response to an adequate dose (as much as 1,500 mg per day) of levodopa in a formulation that includes carbidopa, the absence of atypical features, and no evidence for other parkinsonian disorders or causes of secondary parkinsonism (discussed later). Even with this in mind, the diagnosis can still be difficult in elderly patients—those 65 years of age and older—because there are many causes of tremor, postural instability, and gait disturbances in the elderly.

Tremor in an older patient may be due to medication, metabolic disturbances such as hyperthyroidism, Parkinson's disease, or essential. Characteristics such as asymmetry, tremor occurring at rest and decreasing with use of the affected limb, and especially a pill-rolling type of tremor when the fingers are involved point to Parkinson's disease. Sometimes this last characteristic can be elicited by asking the patient to walk or distracting the patient by requesting he or she do simple calculations. Parkinsonian tremor may involve the head, the lips, the tongue, and the jaw. Some patients with Parkinson's disease have a notable action component to their tremor. Because tremors are additive, differentiating Parkinson's disease from essential tremor can be a challenge, particularly early in the course of the disease. Features of essential tremor include absence at rest, an increase with stress or excitement, head or voice involvement, onset at an early age, and a family history. Of note, 15% of patients with Parkinson's disease also have an increase in their tremor with excitement, a tremor that involves the head or voice, an early age at onset, and a family history. Careful attention to details in the history and physical examination will help to distinguish these two disorders.

Gait disturbances are common in elderly persons, affecting as many as 15% of people older than 60; in fact, 25% of persons older than 80 use ambulatory assistive devices. There are many causes of gait disorders and postural disturbances, and thus physicians need to observe a patient's gait carefully and note the abnormal and normal features. A parkinsonian gait is characterized by a flexed posture, diminished or absent arm swings, small steps, en bloc turning (turning with little or no rotation of the axial skeleton), difficulty initiating gait and turning, and festination. Gait abnormalities accompany many diseases and may be mistaken for Parkinson's disease. An apraxic gait is characterized by shuffling, hesitation in starting (the feet may appear glued to the floor), poor standing balance, and improvement after the first few steps. Gait apraxia is usually caused by bilateral frontal lobe lesions due to multiple infarcts, degenerative processes such as Alzheimer's disease, or hydrocephalus. A spastic gait is a stiff-legged gait with reduced toe clearance (there is some plantar flexion in the feet that may superficially appear like footdrop) and circumduction associated with bilateral spastic weakness of the legs. It can be caused by spinal cord compression, subacute spinal cord degeneration in vitamin B_{12} deficiency, or brain tumors involving bilateral parasagittal areas. A steppage gait, where a patient lifts the feet higher than normal and then strikes the ground heavily with each step, is the result of diseases causing an impairment of the position and joint sense in the legs and feet (usually a peripheral neuropathy involving large sensory fibers) such as vitamin B_{12} deficiency, tabes dorsalis of neurosyphilis, and other disorders that cause dysfunction of the posterior columns of the spinal cord.[8]

Other Parkinsonian Disorders

Although most patients with clinical features of parkinsonism have Parkinson's disease, a few have other

neurodegenerative disorders that have parkinsonian features. Differentiating these disorders from Parkinson's disease can be difficult and depends on the presence of other additional characteristic clinical findings. Hence, these diseases are often referred to as "parkinsonism plus" syndromes. Four fairly well characterized syndromes are progressive supranuclear palsy, the Shy-Drager syndrome, striatonigral degeneration, and olivopontocerebellar atrophy. These are sometimes referred to as multiple system atrophy because they involve various nervous systems and patients may present with any combination of extrapyramidal, pyramidal, cerebellar, and autonomic symptoms.[6]

Progressive Supranuclear Palsy

Progressive supranuclear palsy occurs more often in men and about ten years later than Parkinson's disease does on average. The earliest symptoms are gait and balance impairment: in contrast to patients with Parkinson's disease, the gait is stiff and broad-based, with the knees and trunk extended rather than flexed. Instead of turning en bloc, patients tend to pivot. The most distinguishing feature is paralysis of the downward gaze, resulting in difficulty reading and feeding (patients are often described by others as "sloppy eaters"). Patients are unable to converge their eyes, and loss of upward and lateral eye movement later develops as well. Other features include palilalia (repetition of syllables), stuttering, and pseudobulbar symptoms such as dysarthria, dysphagia, and emotional lability. Mild dementia may be present in the early stages of disease. Computed tomography and MRI typically show generalized and brain stem atrophy. Treatment success with antiparkinsonian drugs is poor, and treatment is best left to a neurologist.

Shy-Drager Syndrome

The Shy-Drager syndrome, also known as multiple system atrophy, is characterized chiefly by a loss of autonomic function out of proportion to parkinsonian features. Two subtypes of multiple system atrophy can be distinguished: predominant striatonigral degeneration with bradykinesia and rigidity out of proportion to resting tremor, and an olivopontocerebellar atrophy with prominent truncal ataxia, intention tremor, and slurred speech. Most patients show an overlap of the two symptom constellations. Orthostatic hypotension, bladder incontinence, and impotence are often presenting features. Bowel incontinence, emotional lability, severe obstructive sleep apnea, and vocal cord paralysis with stridor are often seen in more advanced stages. An MRI often shows areas of decreased signal bilaterally in the posterolateral putamen. Treatment is mostly symptomatic.

Striatonigral Degeneration

Striatonigral degeneration can be similar to Parkinson's disease. Differentiating features include an absence of tremor (an important distinguishing feature), an early onset of falling, severe dysarthria and dysphonia, excessive snoring and sleep apnea, hyperreflexia, and extensor plantar responses. Patients typically show a poor response to levodopa.

Olivopontocerebellar Atrophy

Olivopontocerebellar atrophy has cerebellar ataxia as its distinguishing feature and progressive parkinsonism as a less dominant feature. Gaze impairment, dysarthria and dysphagia, incontinence, dementia, and both upper and lower motor neuron signs occur as the disease progresses. Computed tomographic and MRI scans typically show pancerebellar and brain stem atrophy and demyelination of transverse pontine fibers. The response to levodopa treatment is poor.[9]

Secondary Parkinsonism

Secondary parkinsonism is caused by drugs, for instance, antiemetics (metoclopramide and prochlorperazine), antipsychotics (haloperidol and chlorpromazine), reserpine, methyldopa, and lithium; encephalitis; vascular disease (multiple infarcts); trauma; normal-pressure hydrocephalus; and toxins, such as carbon monoxide poisoning, mercury, manganese, methanol, ethanol, and notably methylphenyltetrahydropyridine (MPTP). This last-named compound is a meperidine-like "designer drug" that causes clinical and pathophysiologic disease similar to Parkinson's disease.[9]

Whereas the diagnosis of Parkinson's disease can be straightforward, it can also be difficult. Careful attention to the clinical abnormalities during the physical examination, with particular attention to any atypical features, and a thorough medical, occupational, and medication history, both past and present, will help differentiate Parkinson's disease from "Parkinson's plus" syndromes or secondary parkinsonism. Any doubts about the diagnosis should be allayed by consultation with an experienced neurologist.

Treatment of Parkinson's Disease

If the symptoms are mild and do not cause any substantial impairment in a patient's activities of daily living and work, then medical treatment may be withheld until the symptoms progress further.

An alternative approach is to start treatment with the monoamine oxidase (MAO) type B inhibitor selegiline hydrochloride once the diagnosis is made. Selegiline may exert a neuroprotective effect by reducing the amount of hydrogen peroxide and free radicals generated by the breakdown of levodopa by striatal MAO type B. This hypothesis was proposed after studies of animals showed that selegiline blocked the metabolism of MPTP and prevented the development of parkinsonism. The use of selegiline as a neuroprotective agent began when the preliminary results of a large multicenter study, the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) study, showed that patients treated with selegiline progressed substantially less than did those given placebo. (The DATATOP study also showed that vitamin E had no neuroprotective effects.) When the final results of the DATATOP study were pub-

lished in 1993,[10] however, whether selegiline was actually neuroprotective was less clear because it exerted a mild symptomatic effect that may have been interpreted as less progression. Recently published results of extended treatment of DATATOP subjects converted to treatment with open-label deprenyl failed to show any notable neuroprotective effect.[11,12] Yet, another separate study did show a benefit of the use of deprenyl on the progression of Parkinson's disease.[13] Thus, this issue remains controversial. Many neurologists advocate offering selegiline as monotherapy in the early stage of the disease or at least to use concomitantly with levodopa in patients being started on levodopa therapy[9]—after discussing with the patient its possible benefit, the current lack of more definitive proof, and its substantial cost.[14,15] The common side effects of selegiline use are insomnia (its metabolites are L-amphetamine and L-methamphetamine) and dysphoria; psychotic episodes can occur in elderly patients. The usual dose is 5 mg at breakfast and lunch; no dietary tyramine restriction is necessary because at this low dose, selegiline inhibits only MAO type B. The use of meperidine should be avoided in patients taking selegiline, however, because of possible fatal interactions with MAO inhibitors.[16]

Symptomatic treatment should be started once the disease progresses to the point where a patient's ability to work or perform activities of daily living is impaired. Levodopa has proved to be the most effective drug for treating patients with Parkinson's disease. Initially, there was some theoretical concern that its administration might lead to increased free radical production and hence increase the rate of disease progression. This consideration led to the withholding of levodopa therapy for as long as possible. As more long-term experience accumulated with patients taking levodopa, it became evident that this theoretical concern was not seen clinically. The current recommendation is that levodopa treatment should be started as soon as necessary.[2,14,15]

In North America, levodopa is combined with the peripherally acting dopa decarboxylase inhibitor carbidopa as Sinemet (DuPont Pharmaceuticals). Carbidopa blocks the peripheral conversion of levodopa to dopamine, which allows the delivery of more levodopa to the brain and also reduces the incidence of nausea, the major side effect of peripheral dopamine. At least 75 to 100 mg of carbidopa daily is necessary to counteract levodopa-induced nausea. Hence, it is preferable to start treatment with 25-100 tablets (25 mg of carbidopa per 100 mg of levodopa) rather than the 10-100 formulation. Therapy should begin with half a tablet of 25-100 Sinemet taken three times a day 30 to 60 minutes before meals. If the patient experiences intolerable nausea, then it can be taken with or after meals. Although the efficacy of levodopa will be substantially reduced by decreased absorption through interference from dietary protein, this may result in less frequent nausea. Once a patient adapts to the drug, it should then be taken before meals again to maximize absorption and hence ensure the chance of an adequate response. The onset of action usually takes place within an hour, and most patients know within three days whether a new dosage regimen is working (it may take as long as 7 days in elderly patients). Dosages can be increased every three to five days (weekly in an elderly patient) until sufficient improvement is achieved. Because carbidopa is a noncompetitive inhibitor of dopa decarboxylase, no benefit is attained with doses of carbidopa greater than 200 to 300 mg, and thus patients requiring high doses of levodopa should be switched to the 25-250 formulation. Once a levodopa dose of 600 to 800 mg per day is reached, adjunctive medications are preferable to further increases of levodopa.[16,17] Sinemet CR, a controlled-release formulation, can also be used as initial therapy, starting with half a tablet of the 25-100 formulation twice a day. Note that the bioavailability of the controlled-release formulation is about 30% less than the standard formulation, so a patient being switched to a controlled-release formulation may require a 30% increase in dosage to achieve the same clinical effect.

In patients who achieve good clinical response at low dosages of levodopa—doses insufficient to provide at least 100 mg per day of carbidopa—and who have considerable nausea, taking supplemental carbidopa three to four times a day may prove helpful. For others having nausea at reasonable carbidopa doses, controlled-release formulations may be better tolerated owing to the slower rise and lower peak concentrations achieved. Domperidone has been effective in ameliorating nausea in this setting, but the drug is not yet approved for use in the United States. Drugs such as metoclopramide and prochlorperazine should be avoided because they can counteract the central effects of levodopa.

Other side effects of levodopa include postural hypotension (in as many as 20% of patients), confusion, vivid dreams and nightmares, paranoia, and outright psychosis (especially in the elderly). Adverse psychiatric effects usually begin nocturnally, so reducing, stopping, or giving the last evening dose earlier may help; in general, the use of neuroleptic drugs is contraindicated because they may induce a protracted worsening of parkinsonism.[17]

Amantadine hydrochloride has been used in the past to treat Parkinson's disease; its precise mode of action is unknown. The efficacy is modest compared with that of levodopa, but it may be effective in patients with mild disease. Amantadine may begin to lose its effectiveness in 6 to 12 months, however. The usual dose is 100 to 200 mg a day. Side effects include dry mouth, constipation, insomnia, and other effects similar to those of anticholinergics. Particular to amantadine are pedal edema and livedo reticularis.[14,17]

Anticholinergic drugs, such as trihexyphenidyl hydrochloride, 6 to 15 mg per day; benztropine mesylate (Cogentin), 1 to 6 mg per day; biperiden hydrochloride (Akineton), 2 to 10 mg per day; and procyclidine hydrochloride (Kemadrin), 7.5 to 20 mg per day, are useful for treating the tremor of Parkinson's disease. They may be useful as monotherapy in early disease when tremor is the predominant symptom, or as adjunctive

therapy in more advanced disease in patients whose tremor is poorly controlled by levodopa. Side effects are dose-related and tend to be greater than those of levodopa. The anticholinergic side effects include constipation, urinary retention, blurred vision, impaired memory, hallucinations, and acute confusion; these problems are especially more common in elderly patients, and thus great care must be exercised when administering these drugs. Trihexyphenidyl and benztropine are the more potent anticholinergics, but some patients failing to improve with these may respond to the use of others.[5,18]

Adjunctive Therapy

Dopamine Agonists

Dopamine agonists directly stimulate the postsynaptic dopamine receptors and have proved to be useful adjuncts in patients taking levodopa. Their use can allow clinical effectiveness to be achieved with lower doses of levodopa, and motor fluctuations in patients on long-term levodopa therapy can be smoothed over. Many neurologists advocate starting adjunctive dopamine agonist medication when the daily dose of levodopa reaches 600 mg because early use can lead to sustained benefit and a reduced incidence of later motor fluctuations and dyskinesias.[15–17] The side effects of dopamine agonists are more common and more severe than those of levodopa. They include nausea, orthostatic hypotension, and psychiatric disturbances (especially in the elderly and patients with cognitive dysfunction) such as hallucinations, nightmares, agitation, paranoia, and psychotic episodes. Other less common side effects include erythromelalgia and pleuropulmonary and retroperitoneal fibrosis.[18] Monotherapy with dopamine agonists has been investigated and found to be less effective than levodopa, but some neurologists advocate their use as initial therapy in younger patients who are better able to tolerate the side effects. The hope is to delay initiating levodopa treatment due to the later development of management problems in patients on long-term levodopa therapy. The two dopamine agonists currently available in the United States are bromocriptine mesylate (Parlodel) and pergolide mesylate (Permax). Bromocriptine therapy is started at half a 2.5-mg tablet once a day, titrated upward every three to five days to a dose of 5 to 7.5 mg three times a day, with a maximum of 60 mg a day. Effective response is usually attained at 15 to 30 mg a day. Higher doses usually result in more pronounced side effects. Similarly, pergolide therapy is started at 0.05 mg once a day and titrated upward every three to five days to a three-times-a-day dosing regimen until the usual therapeutic dose range of 1 to 6 mg a day. More side effects occur when daily doses exceed 4 mg a day. Studies comparing bromocriptine use with that of pergolide seem to show that pergolide retains effectiveness for a longer time.[19]

Monoamine Oxidase Type B Inhibitors

As mentioned before, the MAO type B inhibitor selegiline may provide a neuroprotective effect when used alone or in conjunction with levodopa. It can also be used as an adjunct to achieve a response with a lower dose of levodopa and to smooth over the "wearing-off" and on-off motor response fluctuations in more advanced disease. The benefits are modest, however.[18,20]

Physical and Occupational Therapy

Physical therapy is an important adjunct in the treatment of Parkinson's disease. Although few studies have rigorously assessed the clinical benefit of physical therapy, many neurologists think that it does improve patients' quality of life and mobility. Specific exercises tailored to each patient's disabilities and needs help mitigate stiffness and slowness and prevent disuse atrophy, weakness, and the deterioration of fine motor control. Appropriate regimens can be designed to maintain mobility, flexibility, stamina, and strength; gait training helps with postural instability and decreases the likelihood of falls.[5] Patients need to be seen by physical therapists routinely to encourage them to maintain their exercises because, if left on their own, they gradually resume a more sedentary lifestyle and stop doing the exercises. The benefits gained from physical therapy are thus lost within six months.[21]

Occupational therapy helps patients maintain more independence by helping them continue their activities of daily living. Patients' homes should be assessed by physical and occupational therapists for the installation of aids such as strategically placed railings, special toilet seats, safety equipment for the bathroom, and specially designed eating utensils and kitchenware. A patient's ability to self-dress can be improved with clothing that has zippers or Velcro closures, and shoes should be the slip-on type with soles that do not grip the floor too tenaciously (causing the patient to fall forward).[5]

Progression of Disease

After several years (typically about 5) of levodopa treatment, the disease progresses to the point where patients begin to have shortened responses to levodopa, often manifesting as a wearing-off phenomenon wherein their symptoms worsen before the next dose of levodopa is due. They may also respond less predictably to each dose and may become extremely sensitive to dietary protein, giving a history of becoming immobilized after eating a high-protein meal. Gastric emptying, which is erratic in patients with Parkinson's disease, can also account for response fluctuations. The wearing-off phenomenon may be lessened by more frequent dosing and taking the medication on an empty stomach; a diet in which the amount of protein eaten is reduced and is saved until the last meal of the day may allow the patient to maintain mobility during the day and be less bothered by increased rigidity and bradykinesia in the evenings when patients are more sedentary.

As the disease progresses further, patients may begin to have unpredictable periods of suddenly becoming immobilized, even in the midst of a good medication effect—an on-off phenomenon. This problem may not

respond as well to dietary measures, so selegiline may be tried instead (if the patient is not already taking it). Dopamine agonists are more effective and can be added if the motor fluctuations are more severe. Controlled-release Sinemet may also be effective in smoothing over response fluctuations and can be used with judiciously timed standard Sinemet to counter the wearing-off and on-off phenomena.[15,16,22]

As the disease progresses and increasingly higher doses of levodopa are used, dyskinesias may develop in the form of athetosis, chorea, and choreoathetosis, which when severe, can resemble ballismus. Lowering the doses of levodopa to reduce peak concentrations and increasing the dosing frequency or adding controlled-release Sinemet may lessen these dyskinesias, but note that drug-induced dyskinesias may result from either too much or too little levodopa. Patients may also have painful dystonias that usually involve the feet and lower legs when levodopa levels ebb before the next dose. Dystonias are common early in the morning and can awaken a patient; taking a controlled-release Sinemet at bedtime may help. Adding a dopamine agonist or increasing its dose may help lessen dyskinesias and dystonias; switching from bromocriptine to pergolide or vice versa may also help. Patients experiencing pain from the dystonias may have some relief with the use of baclofen, lithium, or muscle relaxants.

Patients with advanced Parkinson's disease who are having substantial levodopa-induced dyskinesias and disabling akinetic-rigid states may be candidates for stereotactic pallidotomy, whereby a small area of the internal segment of the globus pallidus is ablated through a stereotactically guided microelectrode introduced through a small burr hole. Recent studies have shown a considerable reduction in levodopa-induced dyskinesias and a lessening in rigidity, bradykinesia, imbalance, and tremor lasting at least a year postoperatively and with relatively low complication rates.[23–25]

As the disease progresses from the early mild stages, other problems become more prominent. Depression, which may be endogenous or reactive, can be present in more than 50% of patients. Many are depressed over the loss of their independence and function, increasing dependence on family and others, and the progressive nature of their disease. They can lose their drive, initiative, and motivation and become passive, withdrawn, and anhedonic. For those who complain of a lack of energy, serotonin reuptake inhibitors such as fluoxetine, paroxetine, or sertraline can be effective. For patients with difficulties sleeping, taking tricyclic antidepressants can be beneficial, especially because their anticholinergic properties may further reduce tremor.[16,26]

Dementia occurs in 15% to 20% of patients with Parkinson's disease and usually develops late in the course. Of note, however, is that as many as a third of patients with Alzheimer's disease can have extrapyramidal signs and symptoms. The presence of dementia early in the course of a patient with parkinsonism should lead to a consideration of Alzheimer's disease (sometimes referred to as Alzheimer's disease with parkinsonism), diffuse Lewy body disease (which some consider to be a variant of Alzheimer's disease), or progressive supranuclear palsy.[5,9]

Drooling may become a problem as the disease advances because of decreased automatic swallowing. Patients often lose weight due to a variety of factors, and constipation can become a serious problem for many, causing a preoccupation with bowel function. Adequate dietary fiber and liquids are important, and promotility agents such as cisapride may be helpful for more severe cases. Bladder hyperspasticity may develop as well as bladder outlet obstruction. Autonomic dysfunction in advanced stages can manifest as sweating, orthostatic hypotension, impotence, constipation, and urinary bladder dysfunction.[16]

Sorting out these problems can be challenging because many of the medications—especially those with anticholinergic properties—can cause hallucinations, confusion, impaired memory, constipation, and urinary retention as well, especially in elderly patients and in those with existing cognitive dysfunction.

Primary Care

Primary care physicians play a central role in the overall care of patients with Parkinson's disease. At the time of the initial diagnosis, patients and family need help in learning about and understanding the disease and its progressive course. They also need reassurance that severe disability usually occurs many years later and that a reasonable quality of life can be maintained with medication, exercise, and continued social activities. Physicians can help to counter the tendency toward immobilization and apathy by encouraging patients to contact national Parkinson's disease organizations, such as American Parkinson's Disease Foundation, 1250 Hyland Boulevard, Staten Island, NY 10305 ([800] 223-2732); National Parkinson's Disease Foundation, 1501 Northwest Ninth Avenue, Miami, FL 33136 ([800] 433-7022); and Parkinson's Disease Foundation, 710 West 168th Street, New York City, NY 10032-9982 ([800] 457-6676), for information about local support groups and newsletters. Referrals for physical and occupational therapy should be made periodically as the disease advances. Speech therapy is beneficial for those with difficulty swallowing and speech problems. In more advanced stages, attendance at a senior day care center is recommended because many centers provide social activities, physical and occupational therapy, and meals for patients. Visiting home nurses and physical and occupational therapists can help improve a patient's activities of daily living, and these professionals can also evaluate the home for safety and make appropriate adaptations of household furnishings. Because caring for patients with more advanced disease can be extremely taxing for spouses and families, respite care should be offered periodically.

In addition to managing other health problems—cardiac disease, diabetes mellitus, hypertension, and the

like—primary care physicians should not overlook routine immunizations and screening because many patients with Parkinson's disease will live for decades after the disease occurs.

In summary, primary care physicians should be knowledgeable about the cardinal features of Parkinson's disease. Treatment can be started in those who meet many of the criteria; failure to respond to adequate doses of levodopa, the presence of any atypical features, or any doubt about the diagnosis should lead to a consultation with an experienced neurologist. In more advanced disease and in patients taking many antiparkinsonian medications, they will benefit from the experience of a neurologist in the management of the disease and from a primary care physician's overall management of their health problems, both related and unrelated to the disease.

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This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the series' editors.

STEPHEN J. McPHEE, MD
TERRIE MENDELSON, MD
Assistant Editors

Commentary

Academic Physicians, Clinical Investigators, and Managed Care
Whither Hippocrates?

WILLIAM M. BENNETT, MD, *Portland, Oregon*

This article is based on Presidential Comments made to the Western Association of Physicians, Carmel, California, February 1996.

It has been my distinct pleasure to serve as President of the Western Association of Physicians since February 1995. I could select from many subjects for a presidential perspective in this era of dramatic advances occurring in the science of medicine in parallel with what are equally dramatic steps backward in the way medicine is practiced. Instead, I will share some thoughts about the unique role of academic physicians and clinical researchers, including their ethical precepts and achievements.

To anyone who reads the lay press, it is obvious that medicine is no longer perceived in the same favorable light as it was a generation ago. This is true despite incredible advances in biomedical science brought about through basic biomedical research, much of which was carried out at the bench and translated to the bedside by physician investigators such as those represented by this association. The improvement in age-adjusted mortality over this period from 1950 to the present is staggering, considering that the manipulation of "risk factors" is relatively recent (Figure 1). I believe that these changes are more likely related to improved patient care. We need only to think of the fact that today, coronary artery bypass surgery can be done with less than 1% mortality; that heart, kidney, and liver transplant graft survival from unrelated donors approaches 90% at one year; that recombinant human erythropoietin is used routinely in medical practice; and that diseases such as leukemia and other formerly fatal cancers have high remission rates and even cures. It is possible to go on and on about the achievements of medical science and medical research. Yet, policymakers, the public, and even leaders in medicine are dissatisfied. They talk about the fact that medical care is too expensive. Is medical care really too expensive, or is too much being taken in profit or spent on marketing and administration? John Kitzhaber, MD, the physician-governor of Oregon, recently uttered the following statement at the Oregon meeting of the American College of Physicians, "The Hippocratic Oath is outdated for the 20th century," in defense of the priority list of the controversial Oregon Health Plan. Dr Kitzhaber was discussing the ethical dilemmas faced by physicians in providing the best medical care for individual patients.[1] Merwyn Greenlick, PhD, Chair of the Oregon Health Sciences University Department of Public Health, talks about a new paradigm for providing medical care, "population medicine," again as opposed to the traditional doctor-patient relationship (oral communication, October 1994). If this euphemism that presumably means doing the greatest good for the greatest number of people with the dollars available is translated by health care professionals to treating only patients with good prognoses or caring for healthy low-risk people, the results will be disastrous. The concept of managed care has been embraced both as a money-saving device and as a way to implement important preventive services. These trends have led to the assumptions that the quality of medical care is reflected by and can be improved by unproven programs, such as population cholesterol screening,[2] adult immunization programs, and other untested strategies. Physician performance in these managed care systems is measured by "productivity quotas" and other measures having little relationship to physician quality (Figure 2).[3] Further, it is assumed by health maintenance organization administrators and leaders that the medical practitioners needed to carry these types of advances forward are less well-trained physicians or physician extenders who will be cost-effective and will, they also assume, function without decreasing the quality of medical care. While patient satisfaction surveys are marketed and promoted by those providing care in this way, the relatively silent lower income groups are not so sure (Figure 3).[4,5]

It is my view and my message that academic medicine as practiced by physician investigators, particularly in academic settings, has rolled over too easily to these untested assumptions. I am embarrassed to acknowledge

(Bennett WM: Academic physicians, clinical investigators, and managed care—Whither Hippocrates? West J Med 1996; 165:241-244)

From the Department of Medicine, Division of Nephrology, Hypertension, and Clinical Pharmacology, Oregon Health Sciences University, Portland.

Reprint requests to William M. Bennett, MD, Dept of Medicine, Division of Nephrology, Hypertension, and Clinical Pharmacology, Oregon Health Sciences University, 3314 SW US Veterans Hospital Rd, PP Ste 262, Portland, OR 97201-2940.

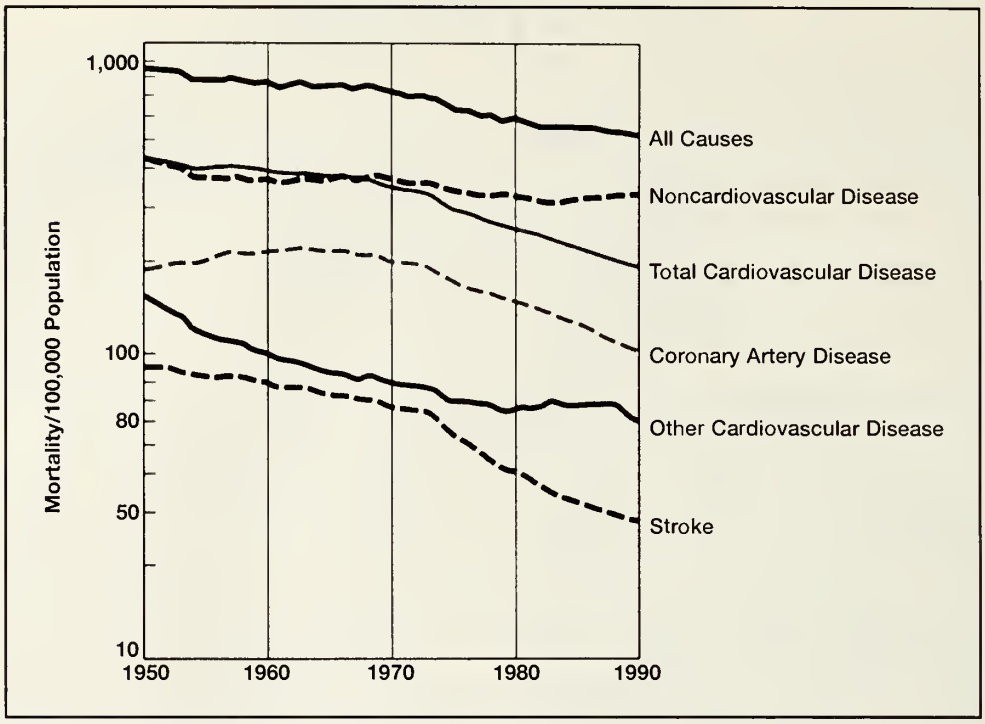

Figure 1.—The age-adjusted mortality in the United States for 1950 through 1990 is shown.

that many of those who have rolled over have been prominent academic leaders whose own career paths to the top were dependent on their contributions as physician-scientists. Can you imagine asking an institutional review board to approve an experiment in which one outcome might be a decreased quality of medical care without asking the permission of patients involved, much less obtaining any type of informed consent? No one would let you do that experiment. Yet, this is precisely what managed care does, without the consent of patients. Does it really make sense for less well-trained physicians and physician extenders to look after patients with complicated medical conditions such as leukemia, organ transplantation, the acquired immunodeficiency syndrome, and oncologic problems, for which specialists and clinical investigators have provided a sophisticated level of medical care that is unparalleled in the world? Is there any situation you can think of in medicine, or with any other form of intellectual pursuit, where reducing the knowledge base of the providers has improved the outcome?

9 measures of quality

5 measures of access to care and satisfaction with care

15 measures of membership and utilization—procedure and hospital admission rates for various conditions

15 measures of finance—loss ratios, liquidity, and financial reserves

15 measures of structure and management—board certification, turnover of physicians, case management, and utilization review

Figure 2.—The content of health plan employer data and information set is shown.

These new trends in the delivery of health care, which have largely gone unchallenged, will create a new minority group, namely, the "seriously ill." Furthermore, in this rush to provide 1996 care more broadly, or more cheaply, no thought is given to money for research or even the training of the next generation of physicians who will be needed to translate the excitement and investment of bench research to the bedside. Managed care pays for none of the freight of its talent while enjoying the largesse of federally supported training programs. There has been a decline of more than 70% in research applications to the National Institutes of Health from physician-scientists in the past several years.[6] Moreover, many of us who have served as program directors in the past several years can attest to the fact that interest in careers in biomedical research by today's young physicians approaches zero. Why should talented persons, who for many years have studied hard and ranked at the top of their classes, select a career path that seems so obviously underappreciated and unsupported by today's society?

Many factors that have accounted for our current situation are clearly beyond our control. But as physicians and physician-clinical investigators interested in our patients and the advancement of medical science, we have some options available. I propose the following actions:

- First and foremost, we can speak out for our patients. When, in our judgment, it is not in a patient's best interest for a medical procedure to be either denied

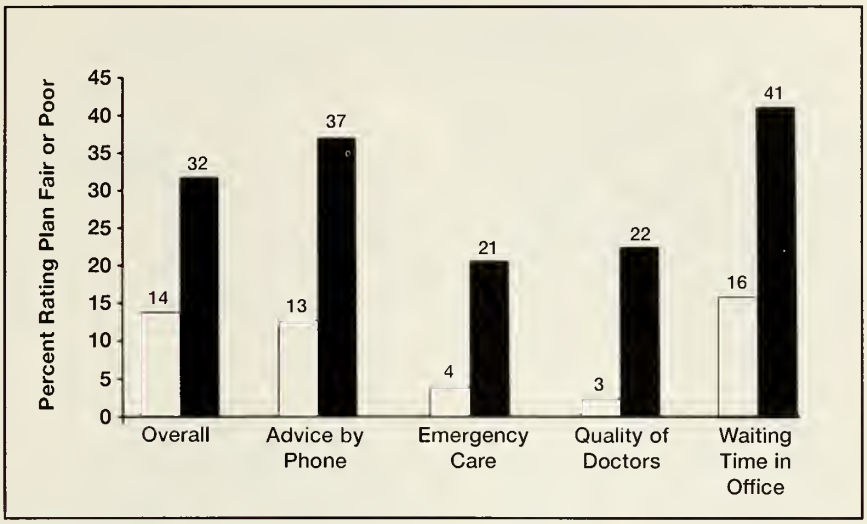

Figure 3.—The experiences of low-income patients (annual income <$15,000) in managed care are shown (from Louis Harris and Associates[5]). White bars = fee-for-service patients, black bars = patients in managed care.

or approved, we must advocate for that patient with the system. No one else will do it. I believe Dr Kitzhaber was mistaken; the Hippocratic Oath is very relevant for the 21st century. We need to watch for and speak out against the inherent conflict of interest whereby incentives are put into medical practice for financial and other reasons dissociated from patients' best interest. Fortunately, Oregon will not ration care because no one there has the political will to "go down the list" of prioritized procedures. There are few data about the long-term financial viability of the Oregon Health Plan (as mandated by law), but there are indications that it is an artistic disaster in deep financial trouble (Julie Ferguson, Vice President, Health Systems and Quality, Physicians Association of Clackamas County), written communication, January 29, 1996). It should be noted that Oregon has been able to ration only for the poor and not the entire state, as planned. In 1991 then-Senator Albert Gore said, "But Oregon has made a tragic choice and a horrible mistake in responding to the plight of the uninsured by developing a scheme that takes from the poor to help the poor, that preys on the limited political clout of poor women and children, and whose only answer to skyrocketing health-care costs is to ration care." The Oregon plan "is a declaration of unconditional surrender just as the first battles are being fought over the future of our health-care system."[7]

• We must continue to advocate for the training and development of basic and clinical investigators. The American Board of Internal Medicine is proposing a shortening of generalist training in internal medicine with an extension of research training, both in basic and clinical science, to produce a generation of subspecialists that can translate the tremendous advances of science to the bedside.[8]

• We should endorse the principal-care concept and disease management organizations. This concept states that an internal medicine specialist or subspecialist can best serve as the primary care physician and coordinate care for patients whose medical condition requires and deserves such subspecialty intervention. Obvious examples are oncologic problems, chronic renal failure, end-stage heart disease, organ transplantation, chronic rheumatoid arthritis, and brittle diabetes mellitus.

• We should mobilize our patients. The patients are the victims of the processes we are discussing, not us. Their children will suffer the consequences of the demise of the biomedical research enterprise in this country and the loss of global leadership in this area that the United States has always enjoyed. Moreover, it is only the patients, not us, who have the political credibility to reverse the current trends. The burden of proof for the throwing away of the past 30 years of medical advances should be shifted to the people who want to do something radically different without any proof of safety and efficacy.

• Physician-clinical investigators need to take a responsible role with the media. We need to educate the next generation of consumers about the processes of science, the pitfalls of "magic bullets," the way new drugs become approved, and all the things that, when twisted by reporters looking for a story, unfairly raise expectations and lead to a loss of confidence in the whole medical enterprise. We need only look as far as the supermarket, the television, and the popular press to see how many billions of dollars, which could be used to provide traditional medical care, are spent on alternative medicines, tonics, vitamins, and herbal remedies.

• If we really want to improve the public health, it might not be done through a medical model at all. The medical problems associated with tobacco, alcohol, and illicit drug use, related domestic violence, and trauma represent the major portion of health care costs.[9,10] If these societal problems were addressed with political

TABLE 1.—*The Health and Financial Effects of Prohibition in the United States**

Variable	*Effect*
Deaths due to overdose and impure alcohol, No.	1,000/yr
Alcohol use in US	Dropped by 50%/yr
Deaths due to cirrhosis	Dropped by 64%/yr
Mental health admissions due to alcohol	Dropped by 53%/yr
Alcohol-related deaths in US, 1992-1995, No.	125,000/yr
Cost of alcohol-related health, motor vehicle accidents, crime, $	140 billion
Taxes collected, $	20 billion

*From M. H. Moore, *The New York Times*, Oct 16, 1989, p A21.

The social contract of American medicine presupposes that physicians are patients' advocates, not advocates for society against patients whose care is costly or patients whose condition is such that physicians cannot be sure that procedures undertaken will have a high likelihood of long-term benefit.

Figure 4.—The ethics against the rationing of medical services by a physician are spelled out (from Burck et al[11]).

will, any appropriate medical care for the sick could be easily afforded. The incidence of these totally preventable medical problems is escalating, however, eroding the nation's limited health care funds. It is of interest to look at the data from the period of alcohol prohibition so reviled by revisionist history. From a public health standpoint, it was a booming success (M. H. Moore, "Actually Prohibition Was a Success," *The New York Times*, October 16, 1989, p A21) (Table 1).[11] Physicians need to stand up and speak out and take an active role in helping to educate and politically influence society to set the practice of medicine back on track.

In conclusion, we need, like no other time in history, to continue to advocate for our patients and to speak out against the rush to make medical care just another product to be sold on the open market. Medicine is not a business. It is a profession with a high calling and ideals that are as relevant today as they have ever been, perhaps more so (Figure 4).[12] If we, who are the leaders in medicine, allow these changes to occur without speaking out, we will be as guilty as the chief executive officers of managed care organizations who sacrifice quality in return for pocketing millions of dollars in salary. This corporate culture of medicine will be the savings and loan debacle of the 1990s.

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Editorials

Barriers to Practice—Reality or Perception?

ELSEWHERE IN THIS ISSUE of the *Journal*, Arlyss Anderson, MHS, RN,CS, FNP, Catherine Gilliss, DNSc, RN,CS, FAAN, and Laurie Yoder, MN, RN,CS, FNP, highlight several oft-reported frustrations of nurse practitioners in California.[1] The most frequently described barrier to practice, however—restrictions on the ability to prescribe medications—was mentioned by only 16% of the respondents. The infrequency of dissatisfaction is remarkable in today's turbulent practice climate and may indicate that this group of health professionals has so far run the gauntlet of health reform and remains relatively unscathed. Nonetheless, fundamental questions about the role of nurse practitioners remain unresolved.

Of concern are Anderson and colleagues' characterization of the California Board of Registered Nursing's records of California-certified nurse practitioners as "not well maintained" and the revelation of its inability to quantify certified nurse practitioners. A meaningful analysis of health workforce data and their use in future policy making require the development of accurate methods to account for and study the practice status of all health professionals in California.

As health care delivery systems strive to address goals of cost containment, access to care, quality, and patient satisfaction, greater emphasis on the use of health professionals other than physicians is a logical exploration. Much remains to be learned before wholesale conclusions can be drawn about how such resources are best deployed.

Nurses have played an important role in a wide array of practice settings, both public and private, and in a number of specialty areas. Their versatility has been not only a selling point, but also a confounding factor in attempts to present an understandable image to other health professionals and the lay public. Disparity in education preparation and titles further confuses those who are unfamiliar with possibilities of baccalaureate and master's preparation and other means of achieving designation as advanced practice nurses, clinical nurse specialists, and nurse practitioners. Assignment to a range of settings even further defies attempts to categorize and define parameters of practice neatly. A nurse practitioner carrying out relatively repetitive functions in well-child examinations and family planning clinics can hardly be compared with one who ventures alone into a remote and unpredictable rural primary care office. Although nurse practitioners are purported to be generally geared toward providing heath care to essentially healthy persons, their use in medically underserved areas often takes them deep into the domain of complex differential diagnosis.

It is no wonder that confusion abounds when attempts are made to address prescribing authority, reimbursement, physician supervision or support, and the public image of nurse practitioners. Without diminishing their well-deserved kudos, the prospect of obtaining equal or better primary care in all respects through professions that require less training, lower salaries, and with low rates of litigation is simply too good to be true. As in all such cases, a large number of variables must be addressed before a more realistic perspective can be attained.

To characterize such an analysis as an economically driven professional "turf battle" is a simplification that belies the complexity of the health care market. As in all evolving systems experiencing growing pains, tension runs high when competition and insecurity are present. Not only do nurse practitioners perceive hostility from physicians, but they also frequently indicate difficulties of acceptance by "regular" nursing staff. Indeed, when professional boundaries are blurred, as they currently are between medicine and nursing, uncertainty may give rise to defensiveness and even paranoia. This is only a piece of the issue, however.

Nurse practitioners are not alone in expressing concerns over reimbursement issues. As payment systems move from one scheme to another, physicians similarly find themselves uncompensated for specified services, disenrolled without explanation from provider panels, and ineligible for specific panels, even when highly qualified. Reimbursement rates continue to be discounted, sometimes resulting in net losses to self-employed physicians who must first meet overhead obligations, including the salaries of their nursing staff. Capitated systems place participating physicians at financial risk and continue to raise concerns about economic incentives to limit services to patients. Not discounting the questions raised by Anderson and coworkers, the issue of reimbursement for health care services is one that needs to be addressed at a broad and fundamental policy level that will, in turn, affect all participants in the health delivery system.

California, in the company of 44 other states, appears to be mainstream in its approach to nurse practitioner prescribing privileges. Whether to expand further the current system is a decision to be based on factors beyond mere convenience, including a philosophical discussion of whether a patient with chronic disease such as diabetes mellitus constitutes an "essentially healthy person" subject to ongoing treatment by a nurse practitioner under current "furnishing" laws. The low incidence of reported problems may indicate inadequate mechanisms for oversight and detection. If prescribing options become more liberal, the current licensing board for registered nurses in California would need to accurately track currently practicing nurse practitioners, identify those who have the appropriate education to prescribe, and also be prepared to assume additional investigative and disciplinary functions inherent in oversight responsibilities.

Before it is reasonably possible to eliminate perceived barriers to practice, much needs to be known about the

best ways to achieve the commonly accepted goals of health care delivery. To that end, consider the following:

- How clearly should the role of nurse practitioners be defined? How do licensing agencies and health delivery systems weigh the extent of past and continuing educational experience and scrutiny of ongoing peer review activities to determine the scope of allowable practice (including prescriptive authority?)
- Where does cost accountability lie? In capitated systems, should nurse practitioners and physicians participate equally in both reimbursement schemes and financial risk?
- To what extent is physician supervision and support necessary for specific aspects of nurse practice? How can medical education better equip physicians and nurse practitioners to work compatibly? When litigation occurs, how is professional liability apportioned?
- Are the purported cost savings real? How do physicians and nurse practitioners differ in their use of diagnostic testing and prescribing practices? How do differing approaches affect the rapidity of definitive diagnosis, specific therapy, and ultimate outcome? Will the drive to equalize salaries for equivalent work diminish the savings over time, as it has in some specialty areas? Will the application of overtime and other special pay that is usually afforded nursing staff, but not physicians, ultimately offset anticipated savings? If the role of nurse practitioners in independent practice increases, will there be attendant costs associated with professional liability insurance and licensing boards? When physician support through telephone consultation, standardized procedure, and other oversight is required, to what extent will it be compensated financially, and how will overall cost be affected?
- Will nurse practitioners as a group embrace underserved areas, or will they, like physicians, reject the relative professional isolation and lifestyle factors? According to Anderson and associates' data, only 10% of surveyed respondents currently practice in rural settings. Will nurse practitioners readily assume 24-hour responsibility for primary care patients in underserved areas, or will additional workforce and costs be necessary for comprehensive coverage? Should the model of health care delivery in rural settings differ fundamentally from that offered in urban and suburban settings?
- How is quality of care best measured, and should such measures be applied to physicians and nurse practitioners alike?

The United States' health care delivery system is entering an era with increased emphasis on universal access to basic services and greater restraint in the application of highly technologic care. The concept of quality is being considered in the context of overall resources to society in a reasonable balance with patient desires, available technology, anticipated outcomes of treatment, and patient satisfaction. Economic forces are in a tremendous state of flux and do not influence all segments of the market or health professions equally. Methods of funding medical education in the future are likely to shift.

Given this unsettled picture, little is to be gained by piecemeal adjustments intended to address the expressed concerns of less than half of those surveyed in a single professional group viewed in isolation. How many similar considerations might be brought to light by other members of the health care team? Although the input of health professionals constitutes an important part of the health care debate, the solution must ultimately take into account all the pieces of a complex puzzle. The current revolution in information management may well offer the necessary tools for analyzing our past and inventing a better future for health care. As more sophisticated data become available, all health professionals will likely need to put aside past assumptions about models of practice and venture into as-yet-undefined relationships for the optimal care of patients.

KAREN M. TAIT, MD
Chair, Health Professions and Licensure Committee
California Medical Association (CMA)
Past Chair, Correction and Detentions Health Care Committee, CMA

Colusa County Health Officer
251 E Webster St
Colusa, CA 95932

REBECCA J. PATCHIN, BSN, MD
Vice Chair, Council on Legislation, CMA
Council on Medical Education
American Medical Association

Department of Anesthesiology
Loma Linda University School of Medicine
Loma Linda University Medical Center
Loma Linda, CA 92354

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Physicians and Nurse Practitioners—Old Conflicts and New Opportunities

THE DRAMATIC CHANGES occurring in the health care industry have exacerbated competition among health professionals, particularly among those who provide the same or similar health care services and who may compete for reimbursement from the same pool of resources. Such competition promises to intensify as health care executives, purchasers, and policymakers continue to wring out excess costs and struggle to improve access and quality.

In their article elsewhere in this issue of the Journal, Arlyss Anderson, MHS, RN, CS, FNP, Catherine Gilliss, DNSc, RN, CS, FAAN, and Laurie Yoder, MN, MPH, RN, CS, FNP, offer some insights into one arena of competition from the perspective of California's nurse practitioners, a growing profession whose scope of practice overlaps into many areas of physician practice.[1] The authors found that nearly half (43%) of California nurse practitioners responding to their survey identified one or more barriers to practice. The article explores four major identified barriers, two of which—restrictions on prescriptive authority and reimbursement—concern Califor-

nia law and public policy. The other two barriers concern the attitudes and knowledge of physicians and the public toward nurse practitioners. The authors conclude that these perceived legal and attitudinal barriers unduly restrict nurse practitioners' ability to provide accessible, competent, and cost-effective primary care.

This article alone does not provide strong enough evidence to change California's laws and public policies. It does, however, add to a substantial body of literature and evidence that has been instrumental in expanding practice authority and guaranteeing direct reimbursement for nurse practitioners across the nation. Furthermore, the authors' findings about perceived interprofessional relations should serve as a call to improve collaboration between physicians and nurses who will increasingly find themselves working together.

Changes in this area of the law have only come after contentious and politically charged battles in state legislatures where scopes of practice are written into statute. "Scopes of practice," a major component of professional regulation crafted to protect the public, describe the authority to practice vested by a state in health professionals and draw boundaries among the individual professions, creating domains of practice control.

Despite some overlap with physicians' scope of practice, nurse practitioners are among many nonphysician professionals arguing that restrictive scopes deny them the right to provide services they are competent to render.[2] In 1995, 300 bills expanding or clarifying scopes of practice and defining reimbursement for nonphysician providers were enacted into law by state legislatures across the country.[3] Legislators who craft scopes of practice must balance regulation's effects on the quality, cost, and accessibility of services with both professional interests and public protection.[4]

Three major arguments are advanced to support the expansion of nurse practitioners' scope of practice. First, studies indicate that within their scope of practice, nurse practitioners provide primary care whose quality is as high as or better than that of physicians.[5(p19),6] Second, economic analysis shows that the failure to use nurse practitioners as fully as possible may result in unnecessary expenditures of between $6.4 and $8.75 billion annually.[7] Finally, in terms of access to care, expanded laws for nurse practitioners are presented as a remedy for the nation's federally designated Health Professions Shortage Areas, geographic areas or populations that have access to fewer than 1 physician per 3,000 persons. This ratio is less than half the ratio recommended under most estimates of requirements for primary care physicians.[8]

Various groups have voiced their opinions about scopes of practice. For example, the Pew Health Professions Commission's Taskforce on Health Care Workforce Regulation maintains that unreasonable legal barriers to nurse practitioner practice unduly restrict the public's choice to a limited number of health professionals out of a larger pool of those who are competent to provide particular services.[9] Other arguments in support of expanded practice and reimbursement include balancing professional and gender equity.

The strongest challenges to the expansion of nurse practitioners' scope of practice rely on questions about the adequacy of knowledge and training, the quality of care delivered, and the overall competence of nurse practitioners. The argument made in favor of using nurse practitioners to remedy primary care access is debated on the grounds that it remains to be seen whether nurse practitioners would respond to the elimination of practice barriers by relocating in California's underserved areas. Finally, the purported cost savings through expanded nurse practitioner use is also questioned; this is not a well-studied area, and the lower salaries may be offset by increases in other areas (P. D. Jacobson, L. E. Parker, and I. D. Coulter, "Nurse Practitioners and Physician Assistants as Primary Care Providers in Institutional Settings," working paper, RAND Corporation, June 1996).

Legislative trends reveal that blurring the historical practice line between medicine and nursing is increasingly acceptable in many states. States still vary considerably in their laws governing nurse practitioners, however, and along this continuum of laws there are polar extremes. Louisiana, for example, does not allow any prescribing authority, independent practice, or direct reimbursement, whereas Maine allows independent prescribing authority (including of controlled substances), independent practice (after 2 years under supervision), and direct reimbursement for both Medicaid and third-party payers. Legal scholars have questioned this inconsistency in state practice laws.[2]

This wide variation in laws and regulations across the country probably contributes to California's nurse practitioners' negative perceptions of their practice environment. As the authors point out, one study showed that only five states have laws and regulations governing nurse practitioners that are more restrictive than California's.[10]

For example, there is a substantial difference between California and other state laws concerning prescribing authority. With the recent passage of Assembly Bill 1077 by the California Legislature, which expands some aspects of prescribing authority for nurse practitioners, California laws remain more restrictive than those in 23 other states. All of these states allow nurse practitioners to prescribe additional classes of controlled substances under physician supervision, and 14 states allow them to prescribe independently.

Interstate differences in law and policy extend to the direct reimbursement of nurse practitioners as well. In 27 states, third-party insurers are required to reimburse nurse practitioners for covered services. California laws and regulations do not facilitate listing nurse practitioners on health maintenance organizations' (HMOs) provider plans or guarantee direct reimbursement.

The perceived attitudinal barrier to practice—the lack of support from physicians—reported by Anderson and co-workers corroborates other studies that have illuminated the difficult collaboration between physicians and nurses.[11] Health professions schools have been broadly challenged to increase interdisciplinary training as a way

to develop the foundation for good working relationships between physicians and nurse practitioners.[12] Such opportunities would enable both groups of students to learn about one another's knowledge, skills, and perspectives, thus creating a foundation for developing the trust and respect essential to effective collaboration between nurse practitioners and physicians.

There is some reason to be sanguine. The results of a recent study of nurse practitioners and physician assistants providing primary care services in HMOs and multispecialty groups suggest that nurse practitioners and physician assistants in these settings have collegial relationships with physicians (P. D. Jacobson, L. E. Parker, I. D. Coulter, working paper, RAND Corporation).

The article by Anderson and colleagues offers a launching pad for at least three further lines of research that would address the degree to which remaining barriers to nurse practitioner practice in California impede efforts to expand access to care, improve the quality of care, and contain health care costs; the effects of restrictions on prescribing authority and reimbursement on the quality and range of health care services nurse practitioners provide in California; and the perceptions of both physicians and nurse practitioners regarding their evolving practice relationships, regulatory realities, and suggestions for improvement.

As systems move to more integrated and managed arrangements for providing health care, they will inevitably raise more questions about who can provide accessible and high-quality services for the lowest costs. The laws and regulations that health care professionals have used to protect the public and their scopes of practice will face important pressures to transform. The resulting tension will play out not only between nurse practitioners and physicians, but between registered nurses and unlicensed assisted personnel, pharmacists and pharmacist technicians, and dentists and dental hygienists. It is our challenge to make this tension creative.

The best reaction to this from the organized professions would be to understand the perspective and value that each brings to providing care and to agree on the broadest possible arena of shared practice, rather than the narrowest. Ultimately, this must lead to innovative and long-term collaborations in practice and regulation that protect and promote the public's health by the most efficient and rational means possible.

LEONARD J. FINOCCHIO, MPH
JANET M. COFFMAN, MPP
CATHERINE M. DOWER, JD
EDWARD H. O'NEIL, PhD
University of California, San Francisco, School of Medicine
Center for the Health Professions
1388 Sutter St, Ste 805
San Francisco, CA 94109-5453

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Parkinson's Disease—A Progress Report

THE SHAKING PALSY described in 1817 by James Parkinson, a general practitioner working in London, is a common neurodegenerative disorder that increases in prevalence with advancing age and is associated with an increased risk of death.[1] It results from the progressive loss of dopaminergic neurons in the substantia nigra of the midbrain, as a consequence of which the striatal concentration of the neurotransmitter dopamine is reduced. Dopaminergic and nondopaminergic cells in other regions are also affected, but loss of the striatonigral projection neurons is the most conspicuous pathologic finding. The cause of this cell loss is obscure. The occurrence of a similar disorder in humans with exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine suggests that toxic exposure is responsible for Parkinson's disease, but no likely exogenous toxin has been identified. An endogenous toxin may be involved. There is evidence that oxidative stress resulting from the metabolism of dopamine is increased,[2] with the formation of free radicals that lead to DNA damage, lipid peroxidation, and cell death. Dopamine is catabolized by monoamine oxidase to 3,4-dihydroxyphenylacetic acid with the generation of hydrogen peroxide, and this in turn may lead to the generation of hydroxyl free radicals. These radicals may be injurious to dopaminergic neurons if the normal protective mechanisms are impaired. Factors influencing the metabolism and distribution of dopamine may therefore be important in the pathogenesis of the disease[2] and are currently under study. There is no evidence, however, that vitamin E, a scavenger of free radicals, exerts any protective effect in patients with Parkinson's disease when taken in daily doses of 2,000 units, although the extent to which it pen-

etrates into the brain is unclear.

The role of heredity in the development of Parkinson's disease is also being reexamined. Early clinical studies of monozygotic or dizygotic twins suggested that genetic factors were not important, but recent studies involving positron-emission tomography have shown the asymptomatic twins of affected patients to have a higher frequency of abnormalities of dopaminergic nigrostriatal function than previously appreciated.[3,4] Work is in progress in several laboratories to identify any genes contributing to the development of the disease.

Over the past decade, it has become clear that the basal ganglia operate as part of functionally distinct parallel circuits that involve the thalamus and cerebral cortex. Several different areas of the cerebral cortex project to the neostriatum, from which there are pathways to the substantia nigra pars reticularis and medial globus pallidus either directly (involving γ-aminobutyric acid [GABA] as neurotransmitter) or indirectly (using GABA-ergic and glutamatergic projections) by the lateral globus pallidus and subthalamic nucleus.[5] The substantia nigra pars reticularis and medial globus pallidus are the main output structures of the basal ganglia and project to the thalamus and thus to the cortex. The precise role of the basal ganglia in motor function remains to be established. It seems, however, that the loss of striatal dopamine results in increased neuronal activity in the pallidal output of the basal ganglia. This, in turn, results in an increased inhibition of thalamic cells projecting to the frontal cortex and thus to reduced motor activity.[5] These concepts have suggested several new therapeutic strategies, which I will discuss.

Treatment of the disorder remains controversial despite the enormous advances of the past quarter century. Elsewhere in this issue of the *Journal*, Don Ng, MD, provides an account for primary care physicians of the general therapeutic approach.[6] It is perhaps worth reiterating that the role of selegiline (a monoamine oxidase B inhibitor) as a neuroprotective agent is uncertain. It is not clear whether selegiline slows disease progression, and studies aimed at clarifying this point have yielded ambiguous or conflicting results. The decision to prescribe this agent, therefore, remains an individual one, requiring the possible but uncertain benefit of treatment to be balanced against the high cost involved and safety concerns fueled by a recent report of increased mortality associated with the use of selegiline.[7] Other monoamine oxidase B inhibitors, such as lazabemide, are undergoing clinical evaluation for any neuroprotective effect, and these studies may provide further guidance for practitioners. It must also be emphasized that complete agreement is lacking on the optimal time and manner for introducing dopaminergic therapy. Many neurologists prefer to start dopaminergic therapy with one of the dopamine agonists rather than with a levodopa-carbidopa combination (Sinemet) because the agonists do not require enzymatic conversion to an active agent and are not metabolized by oxidation, with the generation of free radicals. This approach has the advantage of delaying the development of such side effects as response fluctuations. Ultimately, however, most patients will require combination treatment with Sinemet and a dopamine agonist for benefit. Several new dopamine agonists are undergoing clinical trials, and new methods of administering them are being explored in the hope of obtaining a steadier clinical response.

Novel symptomatic agents are also being evaluated. Selective inhibitors of catechol-*O*-methyltransferase—an enzyme involved in one pathway for the metabolic breakdown of levodopa—may enhance the benefits of levodopa therapy. There are theoretical grounds for thinking that glutamate antagonists will also be helpful in treating parkinsonism by reducing the activity of the subthalamic nucleus, which is driven by glutamatergic output of the motor cortex, and of the glutamatergic connections of the subthalamic nucleus with the substantia nigra and medial globus pallidus. Various neurotrophic factors have been shown in animals to influence dopaminergic nigrostriatal cells, and the development of effective systems for delivering them to the brain may eventually revolutionize the treatment of Parkinson's disease.

Until more effective pharmacologic therapies are developed, operative treatment based on the newly recognized motor circuitry of the basal ganglia should be considered for patients with classic Parkinson's disease who are becoming increasingly disabled despite dopaminergic therapy or who have intolerable side effects of treatment, such as response fluctuations or severe dyskinesias. Pallidotomy (ablation of the globus pallidus) is performed for bradykinesia, rigidity, or postural instability, and thalamotomy for tremor. Other experimental invasive procedures involve high-frequency stimulation of the subthalamic nucleus, thalamus, or globus pallidus, but the mechanisms involved and long-term results of these approaches are unknown.[8] The cerebral transplantation of adrenal medullary or fetal mesencephalic tissue also remains experimental, is undertaken in only a few specialized centers, and has yielded mixed results.

Recent experimental work has provided intriguing fresh insights into an ancient malady and suggested new therapeutic strategies that hold promise for improving the clinical deficit that occurs in Parkinson's disease. Further work is necessary to ensure that the promise becomes a reality.

MICHAEL J. AMINOFF, MD, FRCP
Department of Neurology
Box 0114, Rm M794
University of California, San Francisco, School of Medicine
San Francisco, CA 94143-0114

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A Guide of the Perplexed—Assisted Suicide

As soon as people learn I work in medical ethics, they ask, "What do you think of Jack Kevorkian?" Many physicians, I am sure, get the same question. Some questioners hope to hear the Michigan pathologist praised as a brave hero, others expect him to be condemned as a base buffoon. My answer is that Jack Kevorkian is too sure of himself, too certain of his cause. In the matter of euthanasia and assisted suicide, I think a humble perplexity is the only moral attitude. Melinda Lee, MD, Linda Ganzini, MD, and Kenneth Brummel-Smith, MD, demonstrate some of that perplexity in their article, "When Patients Ask About Assisted Suicide," elsewhere in this issue of the *Journal*.[1] Writing from the only state in the Union that has legally authorized the prescription of lethal doses of medication for terminally ill patients who so request (implementation of which is currently blocked by an injunction), they report that Oregon physicians were "almost evenly split" on the issue of physician-assisted suicide, and they interpret the close vote by Oregon's electorate as a sign of "ambivalence and diverse motives among the voters." My colleagues and I found the same division among Washington State physicians, where an equally close vote disapproved what Oregon voters had narrowly approved.[2] Although a split opinion by physicians and a split vote by the public can mean that those on either side are passionately committed to their positions, it can also suggest that many on the fence just slipped off on one side or another, still unsure which side is right or wrong. Split public opinions may demonstrate split private opinions, and the 48-to-52 split of a poll can echo in the conscience of a person. This perplexity may or may not be empirical fact, but it should be the moral attitude to take in the face of this momentous shift in the ethics of medicine.

One of medicine's greatest physicians, Moses Maimonides of 12th century Cordoba and Cairo, wrote the book *The Guide of the Perplexed*.[3] He wrote not as a physician but as a philosopher and examined with exquisite care such deep questions as the creation of the world and the immortality of the soul. He demonstrated that human reason can clarify much about these questions but is powerless to resolve them. Perplexity is the proper stance of reason before mysteries. Religious faith alone closes the questions. The advice of the great Maimonides is worth recalling in this modern debate. Whereas some physicians adhere to a religious faith that will close the question of assisting death, many others, even the sincerely religious, will not find the final answer. Many physicians will find only the ambiguous conscience that can see both good and bad reasons on both sides of the debate.

Physicians are rarely philosophers and almost never great philosophers like Maimonides. They cannot merely meditate on these problems. They are forced to respond to patients who inquire about their stance and about their willingness to assist. They are now and increasingly will be forced to decide. If they incline toward a yes answer, they will have to learn, as Lee and associates suggest, much more about this new facet of patient care. The psychology of the seriously ill will have to be better understood. The highly subjective quality and quantity of suffering will have to be carefully assessed. The pharmacology of "overdosing" that physicians have assiduously avoided will have to be mastered. The technicalities of the law and regulations that will inevitably surround this practice will have to be correctly interpreted. Kevorkian has hardly been an exemplar for the competent physician willing to assist patients to die.

Even those who incline to the yes side will be faced with agonizing decisions. Each state will have its own law and regulations, but the Oregon statute will serve as something of a model. At present, those who advocate legal authorization tend to avoid the broad formulations of the recent past. Physicians may hasten death only for those conscious and competent enough to ask for help. Further, under the Oregon model, they may only prescribe medication, not administer it. This is the safest legal formulation. Yet, it leaves physicians and families with painful problems. There will be persons whose terminal condition arrives suddenly and without prevision. Unable to ask, they will suffer for long periods. Others will suffer but not be terminal in any technical sense. Some who can request help may be unable to self-administer the prescribed medication. Willing physicians will be constantly tempted to move beyond the law's safe line.

Those physicians who incline to the no side will not be able to shelter themselves from the paradoxes. They may find that patients for whom they have long cared seek help in dying that they cannot conscientiously offer. Such a conclusion to a caring relationship may pain everyone. Unwilling physicians may even feel obliged to inform every new patient of his or her stance long before any situation calls for a decision. Unwilling physicians may find themselves exiles in a health care culture where a willing compliance with requests for assisted suicide is taken for granted.

Perhaps the most perplexing part of this problem will come for those philosophically minded physicians who have thought through the ethics of this matter. There are many arguments in the literature, from the invocation of the Hippocratic Oath to the anticipation of the "slippery slope." Some physicians have considered these arguments closely and evaluated their strengths and weaknesses as justifications for acting or refraining. One of the most persuasive arguments on the side of hastening death was offered by Howard Brody, MD, who argues that the presumptive duty to assist a patient to die easily derives

from the fact that all prior efforts to cure or to palliate have failed.[4] The physician, having brought the patient to this pass by his or her ministration, has a duty to remedy that failure, should the patient request it. In particular cases, assistance in dying is the compassionate response to medical failure and a fulfillment of competent care of the patient.

Although this argument makes some sense, it assumes that the physician and patient have collaborated over the course of the illness and together have reached this therapeutic impasse. We know today that such collaboration is becoming less common. Many patients have no such relation with a physician until they are acutely ill. Many are dying in intensive care units far from their place of residence and usual care and under the attendance of physicians who have not known them. Requests will be made by strangers to strangers. Physicians whose willingness to accede to requests rests on Brody's compassionate thesis will be faced with moral perplexity.

Decisions must be made even in perplexity. Those who must make the decisions must gather all the necessary knowledge, pursue the available options and, in the last analysis, choose the course that appears the lesser evil in the circumstances. Above all, they must never avert their consciences from the perplexity, making what is intrinsically hard seem easy or what is agonizing casual. A recent news story began, "For Dr Jack Kevorkian, Thursday was a fairly normal day. . . . He played a little golf and appeared at a popular lunch hangout. Later that night, he appeared at Pontiac Osteopathic Hospital with the body of a Massachusetts woman, Judith Curren, who had a nervous disorder and chronic fatigue syndrome . . . the 35th person known to die 'in the presence of Dr Kervorkian.'" (J. Lessenberry, "Kevorkian Goes From Making Waves to Making Barely a Ripple," *The New York Times*, August 17, 1996, p A6). I hope that it will never be a "normal day" when a conscientious physician decides or declines to aid a patient to end life.

ALBERT R. JONSEN, PhD
University of Washington
School of Medicine
Box 357120
Seattle, WA 98195-7120

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Correspondence

Out-of-Control Snowboarders

To the Editor: Regarding the article by Terence M. Davidson, MD, and Aristotle L. Laliotis, MD, in the March 1996 issue of The Western Journal of Medicine,[1] an issue of skiing-related injuries that is neglected in this study is the unfortunate occurrence of skiers colliding with other persons. I have had a number of patients under my care who have been severely injured by collisions with out-of-control skiers and snowboarders. One man who was under my care was severely injured after being hit by an out-of-control snowboarder, causing a complex fracture of my patient's leg. The snowboarder in that instance was not hurt, but the snowboard was the instrument of injury.

I would be interested if Drs Davidson and Laliotis have any comments on the frequency of such injuries to bystanders caused by alpine skiers and snowboarders.

SAMUEL A. WISE, MD
3201 S Maryland Parkway, Ste 514
Las Vegas, NV 89109-2427

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* * *

Dr Davidson Responds

To the Editor: The comments by Samuel A. Wise, MD, are appreciated. When snowboarders first entered the alpine ski slopes, many predicted an increase in the number of crashes based on the assumption that alpine skiers and snowboarders travel different courses at different speeds. This fear has not been realized, and in fact, snowboarders are now welcomed at most alpine ski resorts across the United States.

At Mammoth Mountain Ski Resort, there was no increase in the number of crashes between alpine skiers and snowboarders. This is not to say that collisions between skiers and snowboarders are not a problem. Collisions continue to occur, and unfortunately, in these accidents head and facial and more serious injuries are more frequent than with noncollision accidents. Most collisions are alpine skier to alpine skier.

The experience at Mammoth shows that collisions are a risk, and the alpine skiers should be focused on avoiding collisions with other alpine skiers.

There is a worthwhile adage that the ski patrol continually tries to teach—"Control is the goal." If all skiers followed this, the frequency of all types of collisions would decrease.

TERENCE M. DAVIDSON, MD
Division of Otolaryngology–Head and Neck Surgery
University of California Medical Center, San Diego
200 W Arbor Dr
San Diego, CA 92103-8895

Lessons From the Practice

I Owe It All to Jose and His Mother

ELIZABETH T. MATTHEWS, MD, *Albuquerque, New Mexico*

I don't even have to close my eyes to imagine myself back in that inner-city basement clinic. I was a pediatric intern. Jose's mother had brought her son to the United States from Puerto Rico, to me, to get better medical care for her boy.

Jose was 13. He had spastic quadriplegic cerebral palsy. He had contractures and scoliosis, could not speak, lived in his wheelchair, was difficult to feed, and needed suctioning to help with his secretions. And, yet, he was surprisingly healthy. His mother took such good care of him that he had never suffered any pulmonary complications. Not having dealt with children with handicaps, I scarcely knew where to begin. Jose's physical and medical problems seemed overwhelming. Because I didn't know how or where to start, I did the next best thing: I sat down with Jose's mother for a long time and made a list of everything she felt he needed, adding to it myself as we went along. I did a thorough physical examination as if he were any normal child and added more items to the list. Then I sat down again with Jose's mother, organized the items on the list according to their importance, and set to work.

In retrospect, this visit and my subsequent relationship with Jose and his mother were pivotal in my practice of pediatrics. More important than the intellectual challenge was the emotional awareness that Jose's mother awakened in me. I saw her love for Jose, her youngest son. It was not pity, not duty, but absolute love. Jose was transformed from a "complex handicapped patient" to a 13-year-old boy whose mother loved him and who loved her in return. Jose expressed this not in words or gestures, but in every part of his being, and it was obvious to anyone who took the time to look.

Time passed, my internship ended, and my residency began. I saw Jose and his mother regularly. They were a welcome sight in my busy clinic. I met Jose's father and his older brothers during a family conference to discuss the pros and cons of a proposed operation. But most of the time I saw Jose and his mother. At my last visit with Jose's mother, she said she wasn't feeling well and was going to the doctor. A week later, she was dead, of advanced pancreatic cancer. I did not know this until shortly afterwards when Jose showed up in my clinic with his father, who told me the news. The father didn't know what to do with Jose, for he required so much care, and the family couldn't keep up with everything his mother had been doing for him all along. Jose missed her, he said.

Jose developed pneumonia soon thereafter and was admitted to the hospital. I visited him on the ward, and he was so sick. He went into respiratory arrest when I was at his bedside. I resuscitated him and pushed him down the hall to the intensive care unit (ICU), knowing the ICU team would give me a hard time about bringing them a patient whom some would have labeled a "no-resuscitation code." But this was Jose, and Jose was precious.

He made it out of the ICU and was cared for by different teams of residents and nurses. His family couldn't take him home. They had no one to care for him, no one to give him even the basic care he needed, let alone the respiratory treatments he now required. So he remained on the ward, too sick for a nursing home and too much of a burden for home. When I visited him now, I could hardly bear to see him. He was alone and tied to the bed rails so he wouldn't dislodge his oxygen mask. He would turn his frightened, bewildered eyes toward me and cry. I felt I had failed Jose and his mother. I should have been able to protect him from all this, now that his mother was not there to do it. But if she had been there, this never would have happened.

Jose died on the ward a while later. I wrote his family my condolences but never heard from them. I consoled myself that he was finally back with his mother and was no longer suffering alone.

I remain a general pediatrician with a special interest in children with disabilities and chronic illness. I have held different positions and chaired many committees dealing with children with special needs. And when I wonder how my career ended up this way, and not, say, in neonatology or cardiology, I realize that I owe it to Jose and his mother.

(Matthews ET: I owe it all to Jose and his mother. West J Med 1996; 165:253)

From the Infant Evaluation Program, University Affiliated Programs, University of New Mexico School of Medicine, Albuquerque.
Reprint requests to Elizabeth T. Matthews, MD, 1201 Calle Del Ranchero NE, Albuquerque, NM 87106.

Lessons From the Practice

Myopia Revisited

SAMUEL M. CHEN, MD, *Glendale, California*

Losing sight of the forest for the trees" is an adage that applies to many aspects of life. Practitioners of medicine are not immune to shortsightedness, as the following cautionary tale illustrates.

Some time ago, I was asked by a urologist colleague to place percutaneous nephrostomy tubes and possibly ureteral stents in an elderly woman with inoperable pelvic cancer, ureteral obstruction, and uremia. He had hoped to relieve her ureteral obstruction and had attempted, without success, to place ureteral stents transcystoscopically. When I inquired whether further treatment options had been discussed with the patient, he assured me that an oncologist planned to administer chemotherapy once her renal function improved.

I visited the patient. Both she and her husband were elderly, frail, exquisitely polite, first-generation Japanese who spoke virtually no English. Their son, whom I summoned to translate, spoke somewhat halting English, but I thought our communication was adequate. I did not discuss the issue of chemotherapy, but, rather, concentrated on describing the procedure I was asked to perform, along with its attendant risks.

The procedure, although technically demanding and lengthy, was successful. I was able to place bilateral percutaneous ureteral stents and nephrostomy catheters. Hematuria, not unexpected, occurred initially but resolved over time, and the patient's flank pain gradually abated. Her azotemia lessened, and she appeared to feel better. Both she and her husband smiled and nodded as I made my daily rounds. As is customary, once I ascertained her ureteral stents were functioning properly, I removed the nephrostomy tubes to minimize the risk of infection and make her more comfortable. My job completed, I did not see her again.

Not long afterward, I saw the urologist and inquired about the patient. He said there had been a delay in obtaining approval for a formal oncology consultation. Once treatment options were fully discussed, the family opted against chemotherapy.

"Oh," I thought. "At least we helped her, albeit temporarily, by relieving her uremia." Aloud I said, "The stents are still working, aren't they?"

He flashed a sheepish grin. "I took them out," he said.

"What?" I almost shouted. "Why?"

"After everything was discussed with the patient and her family, they decided they didn't want her to go home with tubes in her. So I cystoscoped her and removed them."

The pain and discomfort she had endured, the hours I had spent doing the procedure and in follow-up, the not-inconsequential dose of radiation she and I had both received during fluoroscopy, and the many thousands of dollars in expenses incurred during nearly two weeks in the hospital were for naught. They all could have been avoided had someone fully communicated the various treatment options before hasty decisions were made to address consequences (in this instance, uremia) of a disease, rather than the disease (inoperable pelvic cancer) itself.

Although I may not be that ideal "someone," I have, since that event, made a greater effort to ensure that each patient understands the ramifications of a decision to proceed with a diagnostic or therapeutic procedure that may be the first step down a path he or she may ultimately not wish to take. A respect for a patient's choice necessarily takes precedence over what we physicians may deem advisable. Once in a while, we are wrong. Even when we are not, we must allow our patients—not unlike our children—to make their own decisions about their lives.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

(Chen SM: Myopia revisited. West J Med 1996; 165:254)

Dr Chen is an interventional radiologist in private hospital-based practice in Glendale, California.
Reprint requests to Samuel M. Chen, MD, Glendale Adventist Medical Center, 1509 Wilson Terrace, Glendale, CA 91206-4007.

In Memoriam

California Medical Association

Asregadoo, Edward R., Walnut Creek. Died Jun 18, 1994, aged 74. Graduate of Boston University School of Medicine, 1951. Dr Asregadoo was a member of the Alameda-Contra Costa Medical Society.

Brizzolara, Louis G., Berkeley. Died Oct 11, 1995, aged 79. Graduate of University of California, San Francisco, School of Medicine, 1942. Licensed in California in 1942. Dr Brizzolara was a member of the Alameda-Contra Costa Medical Society.

Brody, Ormond V., San Leandro. Died Aug 13, 1996, aged 71. Graduate of Yale University School of Medicine, 1960. Licensed in California in 1965. Dr Brody was a member of the Alameda-Contra Costa Medical Society.

Collins, George W., Pleasonton. Died March 7, 1996, aged 83. Graduate of Medical College of Wisconsin, 1944. Licensed in California in 1945. Dr Collins was a member of the Alameda-Contra Costa Medical Society.

Johnson, Harald N., Berkeley. Died Aug 28, 1996, aged 89. Graduate of University of Nebraska School of Medicine, 1962. Licensed in California in 1962. Dr Johnson was a member of the Alameda-Contra Costa Medical Society.

Kaplan, Herman, Walnut Creek. Died Dec 30, 1995, aged 68. Graduate of State University of New York at Syracuse, 1963. Licensed in California in 1964. Dr Kaplan was a member of the Alameda-Contra Costa Medical Society.

Knudsen, Harry, Bakersfield. Died Aug 28, 1996, aged 68. Graduate of Oregon Medical School, 1961. Licensed in California in 1965. Dr Knudsen was a member of the Kern Medical Society.

Lockett, Richard B., Jr., Emeryville. Died March 19, 1996, aged 52. Graduate of University of Texas, San Antonio, School of Medicine, 1953. Dr Lockett was a member of the Alameda-Contra Costa Medical Society.

Loquvam, George S., Oakland. Died Jul 11, 1996, aged 80. Graduate of Washington University School of Medicine, 1942. Licensed in California in 1947. Dr Loquvam was a member of the Alameda-Contra Costa Medical Society.

Makower, Melvin L., Berkeley. Died March 18, 1996, aged 82. Graduate of University of California, San Francisco, School of Medicine, 1939. Licensed in California in 1939. Dr Makower was a member of the Alameda-Contra Costa Medical Society.

Ostrander, Charles T., Bakersfield. Died Oct 23, 1996, aged 61. Graduate of UC Irvine School of Medicine, 1966. Licensed in California in 1970. Dr Ostrander was a member of the Kern Medical Society.

Page, Emery P., Berkeley. Died Feb 5, 1995, aged 83. Graduate of University of California, San Francisco, School of Medicine, 1939. Licensed in California in 1939. Dr Page was a member of the Alameda-Contra Costa Medical Society.

Parker, Edward E., Hayward. Died Aug 3, 1996, aged 75. Graduate of Tufts University School of Medicine, 1946. Licensed in California in 1957. Dr Parker was a member of the Alameda-Contra Costa Medical Society.

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Plucinski, Theodore E., Concord. Died Aug 25, 1996, aged 55. Loyola University School of Medicine, 1967. Licensed in California in 1973. Dr Plucinski was a member of the Alameda-Contra Costa Medical Society.

Purvis, L. Martin, Rancho Bernardo. Died Sep 17, 1996, aged 85. Graduate of the University of California, San Francisco, School of Medicine, 1937. Dr Purvis was a member of the San Diego Medical Society.

Reschke, Alfred Walter, Fremont. Died Aug 24, 1996, aged 70. Graduate of University of Illinois School of Medicine, 1953. Licensed in California in 1955. Dr Reschke was a member of the Alameda-Contra Costa Medical Society.

Sledge, Carlos R., Oakland. Died Oct 2, 1996, aged 49. Graduate of Michigan State University School of Medicine, 1977. Licensed in California in 1978. Dr Sledge was a member of the Alameda-Contra Costa Medical Society.

Stephens, Bruce, Alameda. Died Jan 27, 1996, aged 94. Graduate of Stanford University School of Medicine, 1931. Licensed in California in 1931. Dr Stephens was a member of the Alameda-Contra Costa Medical Society.

Von Pohle, William R., Redlands. Died Sep 19, 1996, aged 37. Graduate of Loma Linda University School of Medicine, 1985. Licensed in California in 1986. Dr Von Pohle was a member of the San Bernardino Medical Society.

Wiegand, Bernard D., Berkeley. Died Sep 9, 1996, aged 70. Graduate of Harvard University Medical School, 1954. Licensed in California in 1956. Dr Wiegand was a member of the Alameda-Contra Costa Medical Society.

Wiesinger, Warren, Oakland. Died Dec 1, 1994, aged 84. Graduate of Creighton University School of Medicine, 1938. Licensed in California in 1938. Dr Wiesinger was a member of the Alameda-Contra Costa Medical Society.

Wilcox, Delbert E., Walnut Creek. Died Aug 4, 1995, aged 73. Graduate of University of Wisconsin School of Medicine, 1946. Dr Wilcox was a member of the Alameda-Contra Costa Medical Society.

Young, Fitzroy E., Oakland. Died Jun 2, 1994, aged 91. Graduate of Mehardy College School of Medicine, 1936. Licensed in California in 1943. Dr Young was a member of the Alameda-Contra Costa Medical Society.

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1. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153: 82–86

2. Jones JS, Anderson HW Jr, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444–456

Books

3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press 1966, pp 35–51 [author of book is same as author of chapter]

4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Edition. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456–479 [authors of book differ from chapter author]

Correspondence

5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721–722

Government Publications

6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983

7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522–526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intraarterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

Mass Circulation Publications (Do not include in reference list; put in text)

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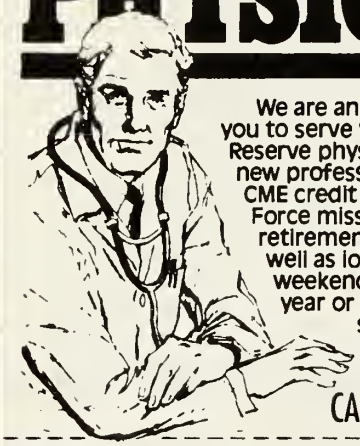

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305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 23-26, 1997, Sun Valley Inn, Sun Valley.

Nevada State Medical Association
3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 1-4, 1997, Sheraton El Conquistador Hotel, Tuscon, AZ.

New Mexico Medical Society
7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 9-10, 1997, Albuquerque, NM.

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PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 11-14, 1997, Jackson Lake Lodge, Moran.

ADVERTISING INDEX

NORCAL MUTUAL INSURANCE COMPANY 179

PFIZER 181

SMITHKLINE BEECHAM
Augmentin . . . . . 2nd Cover, 177

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Special Issues Catalog 185
WJM Subscription Order Form 183
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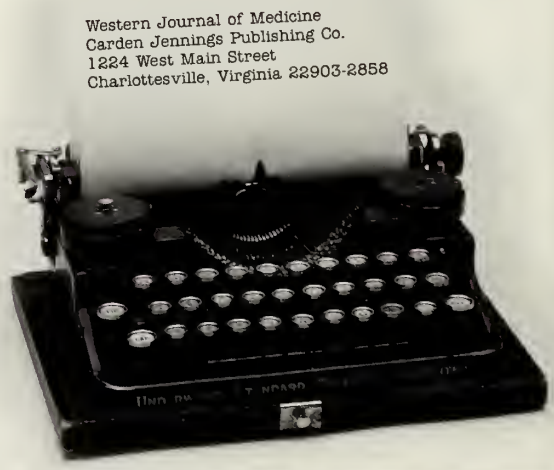

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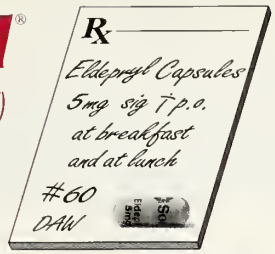

BRIEF SUMMARY Please see package insert for full prescribing information.

INDICATIONS AND USAGE:
ELDEPRYL is indicated as an adjunct in the management of Parkinsonian patients being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy. There is no evidence from controlled studies that selegiline has any beneficial effect in the absence of concurrent levodopa therapy

Evidence supporting this claim was obtained in randomized controlled clinical investigations that compared the effects of added selegiline or placebo in patients receiving levodopa/carbidopa Selegiline was significantly superior to placebo on all three principal outcome measures employed change from baseline in daily levodopa/carbidopa dose, the amount of 'off' time, and patient self-rating of treatment success. Beneficial effects were also observed on other measures of treatment success (e.g., measures of reduced end of dose akinesia, decreased tremor and sialorrhea, improved speech and dressing ability and improved overall disability as assessed by walking and comparison to previous state)

CONTRAINDICATIONS.
ELDEPRYL is contraindicated in patients with a known hypersensitivity to this drug

ELDEPRYL is contraindicated for use with meperidine (DEMEROL & other trade names). This contraindication is often extended to other opioids. (See Drug Interactions.)

WARNINGS:
Selegiline should not be used at daily doses exceeding those recommended (10 mg/day) because of the risks associated with non-selective inhibition of MAO. (See CLINICAL PHARMACOLOGY.)

The selectivity of selegiline for MAO B may not be absolute even at the recommended daily dose of 10 mg a day and selectivity is further diminished with increasing daily doses. The precise dose at which selegiline becomes a non-selective inhibitor of all MAO is unknown, but may be in the range of 30 to 40 mg a day

Severe CNS toxicity associated with hyperpyrexia and death have been reported with the combination of tricyclic antidepressants and non-selective MAOIs (NAROIL, PARNATE) A similar reaction has been reported for a patient on amitriptyline and ELDEPRYL. Another patient receiving protriptyline and ELDEPRYL developed tremors, agitation, and restlessness followed by unresponsiveness and death two weeks after ELDEPRYL was added Related adverse events including hypertension, syncope, asystole, diaphoresis, seizures, changes in behavioral and mental status, and muscular rigidity have also been reported in some patients receiving ELDEPRYL and various tricyclic antidepressants

Serious, sometimes fatal, reactions with signs and symptoms that may include hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuations of the vital signs, and mental status changes that include extreme agitation progressing to delirium and coma have been reported with patients receiving a combination of fluoxetine hydrochloride (PROZAC) and non-selective MAOIs. Similar signs have been reported in some patients on the combination of ELDEPRYL (10 mg a day) and selective serotonin reuptake inhibitors including fluoxetine, sertraline and paroxetine

Since the mechanisms of these reactions are not fully understood, it seems prudent, in general, to avoid this combination of ELDEPRYL and tricyclic antidepressants as well as ELDEPRYL and selective serotonin reuptake inhibitors At least 14 days should elapse between discontinuation of ELDEPRYL and initiation of treatment with a tricyclic antidepressant or selective serotonin reuptake inhibitors. Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses) should elapse between discontinuation of fluoxetine and initiation of treatment with ELDEPRYL.

PRECAUTIONS:
General:
Some patients given selegiline may experience an exacerbation of levodopa associated side effects, presumably due to the increased amounts of dopamine reaction with super sensitive, post-synaptic receptors These effects may often be mitigated by reducing the dose of levodopa/carbidopa by approximately 10 to 30%

The decision to prescribe selegiline should take into consideration that the MAO system of enzymes is complex and incompletely understood and there is only a limited amount of carefully documented clinical experience with selegiline Consequently, the full spectrum of possible responses to selegiline may not have been observed in pre-marketing evaluation of the drug If is advisable, therefore, to observe patients closely for atypical responses.

Information for Patients:
Patients should be advised of the possible need to reduce levodopa dosage after the initiation of ELDEPRYL therapy.

Patients (or their families if the patient is incompetent) should be advised not to exceed the daily recommended dose of 10 mg The risk of using higher daily doses of selegiline should be explained, and a brief description of the 'cheese reaction' provided While hypertensive reactions with selegiline associated with dietary influences have not been reported, documented experience is limited

Consequently, it may be useful to inform patients (or their families) about the signs and symptoms associated with MAOI induced hypertensive reactions. In particular, patients should be urged to report, immediately, any severe headache or other atypical or unusual symptoms not previously experienced

Laboratory Tests:
No specific laboratory tests are deemed essential for the management of patients on ELDEPRYL. Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions:
The occurrence of stupor, muscular rigidity, severe agitation, and elevated temperature has been reported in some patients receiving the combination of selegiline and meperidine Symptoms usually resolve over days when the combination is discontinued This is typical of the interaction of meperidine and MAOIs Other serious reactions (including severe agitation, hallucinations, and death) have been reported in patients receiving this combination (see **CONTRAINDICATIONS**) Severe toxicity has also been reported in patients receiving the combination of tricyclic antidepressants and ELDEPRYL and selective serotonin reuptake inhibitors and ELDEPRYL (See **WARNINGS** for details) One case of hypertensive crisis has been reported in a patient taking the recommended doses of selegiline and a sympathomimetic medication (ephedrine)

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Assessment of the carcinogenic potential of selegiline in mice and rats is ongoing

Selegiline did not induce mutations or chromosomal damage when tested in the bacterial mutation assay in Salmonella typhimurium and in an *in vivo* chromosomal aberration assay While these studies provide some reassurance that selegiline is not mutagenic or clastogenic, they are not definitive because of methodological limitations No definitive *in vitro* chromosomal aberration or *in vitro* mammalian gene mutation assays have been performed

The effect of selegiline on fertility has not been adequately assessed

Pregnancy
Pregnancy Category C No teratogenic effects were observed in a study of embryo-fetal development in Sprague-Dawley rats at oral doses of 4, 12, and 36 mg/kg or 4, 12 and 35 times the human therapeutic dose on a mg/m^2 basis No teratogenic effects were observed in a study of embryo-fetal development in New Zealand White rabbits at oral doses of 5, 25, and 50 mg/kg or 10, 48, and 95 times the human therapeutic dose on a mg/m^2 basis, however, in this study, the number of litters produced at the two higher doses was less than recommended for assessing teratogenic potential. In the rat study, there was a decrease in fetal body weight at the highest dose tested In the rabbit study, increases in total resorptions and % post-implantation loss, and a decrease in the number of live fetuses per dam occurred at the highest dose tested. In a peri- and postnatal development study in Sprague-Dawley rats (oral doses of 4, 16, and 64 mg/kg or 4, 15, and 62 times the human therapeutic dose on a mg/m^2 basis), an increase in the number of stillbirths and decreases in the number of pups per dam, pup survival, and pup body weight (at birth and throughout the lactation period) were observed at the two highest doses. At the highest dose tested, no pups born alive survived to Day 4 postpartum. Postnatal development at the highest dose tested in dams could not be evaluated because of the lack of surviving pups. The reproductive performance of the untreated offspring was not assessed.

There are no adequate and well-controlled studies in pregnant women. Selegiline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers:
It is not known whether selegiline hydrochloride is excreted in human milk Because many drugs are excreted in human milk, consideration should be given to discontinuing the use of all but absolutely essential drug treatments in nursing women

Pediatric Use:
The effects of selegiline hydrochloride in children have not been evaluated

ADVERSE REACTIONS:
Introduction:
The number of patients who received selegiline in prospectively monitored pre-marketing studies is limited While other sources of information about the use of selegiline are available (e.g., literature reports, foreign post-marketing reports, etc) they do not provide the kind of information necessary to estimate the incidence of adverse events. Thus, overall incidence figures for adverse reactions associated with the use of selegiline cannot be provided. Many of the adverse reactions seen have also been reported as symptoms of dopamine excess.

Moreover, the importance and severity of various reactions reported often cannot be ascertained. One index of relative importance, however, is whether or not a reaction caused treatment discontinuation. In prospective pre-marketing studies, the following events led, in decreasing order of frequency, to discontinuation of treatment with selegiline: nausea, hallucinations, confusion, depression, loss of balance, insomnia, orthostatic hypotension, increased akinetic involuntary movements, agitation, arrhythmia, bradykinesia, chorea, delusions, hypertension, new or increased angina pectoris, and syncope Events reported only once as a cause of discontinuation are ankle edema, anxiety, burning lips/mouth, constipation, drowsiness/lethargy, dystonia, excess perspiration, increased freezing, gastrointestinal bleeding, hair loss, increased tremor, nervousness, weakness, and weight loss.

Experience with ELDEPRYL obtained in parallel, placebo controlled, randomized studies provides only a limited basis for estimates of adverse reaction rates. The following reactions that occurred with greater frequency among the 49 patients assigned to selegiline as compared to the 50 patients assigned to placebo in the only parallel, placebo controlled trial performed in patients with Parkinson's disease are shown in the following Table None of these adverse reactions led to a discontinuation of treatment

INCIDENCE OF TREATMENT-EMERGENT ADVERSE EXPERIENCES IN THE PLACEBO-CONTROLLED CLINICAL TRIAL

Adverse Event	Number of Patients Reporting Events	
	selegiline hydrochloride N=49	placebo N=50
Nausea	10	3
Dizziness/Lightheaded/Fainting	7	1
Abdominal Pain	4	2
Confusion	3	0
Hallucinations	3	1
Dry mouth	3	1
Vivid Dreams	2	0
Dyskinesias	2	5
Headache	2	1
The following events were reported once in either or both groups:		
Ache, generalized	1	0
Anxiety/Tension	1	1
Anemia	0	1
Diarrhea	1	0
Hair Loss	0	1
Insomnia	1	1
Lethargy	1	0
Leg pain	1	0
Low back pain	1	0
Malaise	0	1
Palpitations	1	0
Urinary Retention	1	0
Weight Loss	1	0

In all prospectively monitored clinical investigations, enrolling approximately 920 patients, the following adverse events, classified by body system, were reported

Central Nervous System:
Motor/Coordination/Extrapyramidal:
increased tremor, chorea, loss of balance, restlessness, blepharospasm, increased bradykinesia, facial grimace, falling down, heavy leg, muscle twitch*, myoclonic jerks*, stiff neck, tardive dyskinesia, dystonic symptoms, dyskinesia, involuntary movements, freezing, festination, increased apraxia, muscle cramps

Mental Status/Behavioral/Psychiatric:
hallucinations, dizziness, confusion, anxiety, depression, drowsiness, behavior/mood change, dreams/nightmares, firedness, delusions, disorientation, lightheadedness, impaired memory*, increased energy*, transient high*, hollow feeling, lethargy/malaise, apathy, overstimulation, vertigo, personality change, sleep disturbance, restlessness, weakness, transient irritability

Pain/Altered Sensation:
headache, back pain, leg pain, tinnitus, migraine, supraorbital pain, throat burning, generalized ache, chills, numbness of toes/fingers, taste disturbance

Autonomic Nervous System:
dry mouth, blurred vision, sexual dysfunction

Cardiovascular:
orthostatic hypotension, hypertension, arrhythmia, palpitations, new or increased angina pectoris, hypotension, tachycardia, peripheral edema, sinus bradycardia, syncope

Gastrointestinal:
nausea/vomiting, constipation, weight loss, anorexia, poor appetite, dysphagia, diarrhea, heartburn, rectal bleeding, bruxism*, gastrointestinal bleeding (exacerbation of preexisting ulcer disease)

Genitourinary/Gynecologic/Endocrine:
slow urination, transient anorgasmia*, nocturia, prostatic hypertrophy, urinary hesitancy, urinary retention, decreased penile sensation*, urinary frequency

Skin and Appendages:
increased sweating, diaphoresis, facial hair, hair loss, hematoma, rash, photosensitivity

Miscellaneous.
asthma, diplopia, shortness of breath, speech affected.

Postmarketing Reports:
The following experiences were described in spontaneous post-marketing reports These reports do not provide sufficient information to establish a clear causal relationship with the use of ELDEPRYL.

CNS:
Seizure in dialyzed chronic renal failure patient on concomitant medications
* indicates events reported only at doses greater than 10 mg/day.

OVERDOSAGE.
Selegiline:
No specific information is available about clinically significant overdoses with ELDEPRYL However, experience gained during selegiline's development reveals that some individuals exposed to doses of 600 mg of d,l-selegiline suffered severe hypotension and psychomotor agitation

Since the selective inhibition of MAO B by selegiline hydrochloride is achieved only at doses in the range recommended for the treatment of Parkinson's disease (e.g., 10 mg/day), overdoses are likely to cause significant inhibition of both MAO A and MAO B. Consequently, the signs and symptoms of overdose may resemble those observed with marketed non-selective MAO inhibitors [e g , tranylcypromine (PARNATE), isocarboxazide (MARPLAN) and phenelzine (NAROIL)]

Overdose with Non-Selective MAO Inhibition:
NOTE This section is provided for reference, it does not describe events that have actually been observed with selegiline in overdose

Characteristically, signs and symptoms of non-selective MAOI overdose may not appear immediately Delays of up to 12 hours between ingestion of drug and the appearance of signs may occur. Importantly, the peak intensity of the syndrome may not be reached for upwards of a day following the overdose Death has been reported following overdosage Therefore, immediate hospitalization, with continuous patient observation and monitoring for a period of at least two days following the ingestion of such drugs in overdose, is strongly recommended

The clinical picture of MAOI overdose varies considerably, its severity may be a function of the amount of drug consumed The central nervous and cardiovascular systems are prominently involved

Signs and symptoms of overdosage may include, alone or in combination, any of the following drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonos, convulsions, and coma, rapid and irregular pulse, hypertension, hypotension and vascular collapse, precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin

Treatment Suggestions For Overdose: NOTE Because there is no recorded experience with selegiline overdose, the following suggestions are offered based upon the assumption that selegiline overdose may be modeled by non-selective MAOI poisoning. In any case, up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Poison Control Centers are listed in the Physicians' Desk Reference (PDR).

Treatment of overdose with non-selective MAOIs is symptomatic and supportive Induction of emesis or gastric lavage with instillation of charcoal slurry may be helpful in early poisoning, provided the airway has been protected against aspiration Signs and symptoms of central nervous system stimulation, including convulsions, should be treated with diazepam, given slowly intravenously Phenothiazine derivatives and central nervous system stimulants should be avoided. Hypotension and vascular collapse should be treated with intravenous fluids and, if necessary, blood pressure titration with an intravenous infusion of a dilute pressor agent It should be noted that adrenergic agents may produce a markedly increased pressor response.

Respiration should be supported by appropriate measures, including management of the airway, use of supplemental oxygen, and mechanical ventilatory assistance, as required

Body temperature should be monitored closely. Intensive management of hyperpyrexia may be required Maintenance of fluid and electrolyte balance is essential.

CAUTION—Federal (USA) law prohibits dispensing without prescription

References

1. Holly M. Capsules: still the people's choice. *Pharm Exec.* August 1983:44,46-47.
2. Can the appearance of medication improve compliance? *Pharm J.* January 28, 1989;242:98.

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VOLUME 165 • NUMBER 5 NOVEMBER 1996

ARTICLES

279 Sir William Macewen's Visit to California as the First Lane Medical Lecturer—A Centennial Celebration
T M KELLER

283 Serious Mushroom Poisonings in California Requiring Hospital Admission, 1990 Through 1994
J JACOBS, J V BEHREN, and R KREUTZER

289 Evaluation of Cerebrospinal Fluid in Southeast Asian Refugees With Reactive Serologic Tests for Syphilis
D BUCHWALD, A C COLLIER, S A LUKEHART, P KITH, E GOLDSTEIN, and T M HOOTON

CONFERENCES AND REVIEWS

294 Hospital Volume Influences Outcome in Patients Undergoing Pancreatic Resection for Cancer
R E GLASGOW and S J MULVIHILL

EPITOMES

301 Important Advances in Nuclear Medicine

ALERTS, NOTICES, AND CASE REPORTS

308 Acute Renal Failure Complicating Nonfulminant Hepatitis A
U G MCCANN II, F RABITO, M SHAH, C R NOLAN III, and M LEE

311 Intussusception in an Adult
M A MARINELLA and C D CONLEY

TOPICS IN PRIMARY CARE MEDICINE

313 Current Pharmacologic Treatment of Multiple Sclerosis Symptoms
P-B ANDERSSON and D E GOODKIN

EDITORIALS

318 A Primer for Clinicians on Mushroom Poisoning in the West
C W PINSON and A L BRADLEY

320 Advances in the Treatment of Multiple Sclerosis
L B KRUPP

CORRESPONDENCE

322 Itraconazole-Related Amaurosis and Vomiting Due to Digoxin Toxiticy • Isoniazid-Related Fatal Hepatitis • Response

LESSONS FROM THE PRACTICE

324 Nursing and Doctoring
E GOLDSTEIN

326 Relations
N H ROBIN

OTHER FEATURES

269 Subscription Information

273 Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming

328 Classified Advertising

332 Western State Medical Associations' Meetings

Detailed Table of Contents: 268, 270, 272

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology

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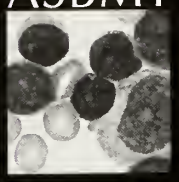

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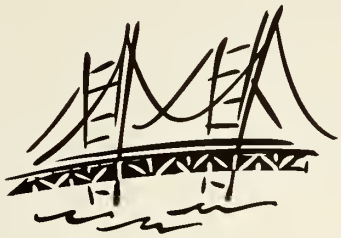

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Diabetic Neuropathic Cachexia

Epitomes, Editorials, Commentary, Lessons From The Practice

The Western Journal of Medicine

VOLUME 165 • NUMBER 5 • NOVEMBER 1996

CONTENTS

ARTICLES

279 **Sir William Macewen's Visit to California as the First Lane Medical Lecturer—A Centennial Celebration**

THOMAS M. KELLER, MD, MPH

From the Pacific Neurosciences Institute, Division of Surgery, University of California, Davis–East Bay, Oakland.

283 **Serious Mushroom Poisonings in California Requiring Hosptial Admission, 1990 Through 1994**

JEFFREY JACOBS, MD, MPH; JULIE VON BEHREN, MPH; and RICHARD KREUTZER, MD

From the California Department of Health Services, Environmental Health Investigations Branch, Emeryville.

289 **Evaluation of Cerebrospinal Fluid in Southeast Asian Refugees With Reactive Serologic Tests for Syphilis**

DEDRA BUCHWALD, MD; ANNE C. COLLIER, MD; SHEILA A. LUKEHART, PhD; PHALLA KITH, PA-C; ERIKA GOLDSTEIN, MD; and THOMAS M. HOOTON, MD

From the Department of Medicine, Harborview Medical Center, University of Washington School of Medicine, Seattle, Washington.

CONFERENCES AND REVIEWS

294 **Hospital Volume Influences Outcome in Patients Undergoing Pancreatic Reseaction for Cancer**

ROBERT E. GLASGOW, MD, and SEAN J. MULVIHILL, MD

From the Department of Surgery, University of California, San Francisco, Medical Center.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Nuclear Medicine

Items of progress in nuclear medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

301 **Radiation Synovectomy**

ERNO J. GYETVAI, MD, and CHARLES W. SUTTER, MD

301 **Radiodosimetry in Nuclear Medicine**

JERROLD T. BUSHBERG, PhD, DABMP

302 **Scintimammography—A New Tool for Breast Cancer Diagnosis**

IRA J. KHALKHALI, MD, FACR, and LINDA DIGGLES, CNMT

303 **Cholescintigraphy in Acute and Chronic Gallbladder Dysfunction**

DAVID K. SHELTON, MD, and ROBERT C. STADALNIK, MD

303 **Role of Lung Scanning in Patients With Pulmonary Embolism**

FRED MISHKIN, MD

(Continued on Page 270)

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WJM1096

(Continued from Page 268)

304 **Use of Bone Mineral Measurements in the Management of Osteoporosis**
JOHN M. VOGEL, MD

305 **Collimation Approaches to 511-keV Imaging**
ALAN D. WAXMAN, MD

306 **Detection and Localization of Gastrointestinal Bleeding**
RHONDA A. WYATT, MD

ALERTS, NOTICES, AND CASE REPORTS

308 **Acute Renal Failure Complicating Nonfulminant Hepatitis A**
ULYSSE G. McCANN II, MD; FELIX RABITO, MD; MISHA SHAH, MD; CHARLES R. NOLAN III, MD; and MAKAU LEE, PhD
From the Department of Medicine, University of Texas Health Science Center, San Antonio.

311 **Intussusception in an Adult**
MARK A. MARINELLA, MD, and CHRISTOPHER D. CONLEY, MD
From the Departments of Internal Medicine and Radiology, University of Michigan Medical Center, Ann Arbor.

TOPICS IN PRIMARY CARE MEDICINE

313 **Current Pharmacologic Treatment of Multiple Sclerosis Symptoms**
PETER-BRIAN ANDERSSON, MBChB, BSC(MED)(HONS),DPhil, and DONALD E. GOODKIN, MD
From the University of California, San Francisco, School of Medicine—Mount Zion Multiple Sclerosis Center.

EDITORIALS

318 **A Primer for Clinicians on Mushroom Poisoning in the West**
C. WRIGHT PINSON, MD, MBA, AND ANNE L. BRADLEY, MD
From the Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Vanderbilt University Medical Center, Nashville, Tennessee.

320 **Advances in the Treatment of Multiple Sclerosis**
LAUREN B. KRUPP, MD
From the Department of Neurology, State University of New York at Stony Brook School of Medicine.

CORRESPONDENCE

322 **Itraconazole-Related Amaurosis and Vomiting Due to Digoxin Toxicity**
LAWRENCE A. CONE, MD, DSc; RONAD B. HIMELMAN, MD; JOEL N. HIRSCHBERG, MD; and JOSEPH W. HUTCHESON, RN

323 **Isoniazid-Related Fatal Hepatitis**
SHELLEY R. SALPETER, MD
PETER S. MILLARD, MD, PhD, and TIMOTHY C. WILCOSKY, PhD, Respond

LESSONS FROM THE PRACTICE

324 **Nursing and Doctoring**
ERIKA GOLDSTEIN, MD, MPH
From the Department of Medicine, University of Washington School of Medicine, Seattle.

(Continued on Page 272)

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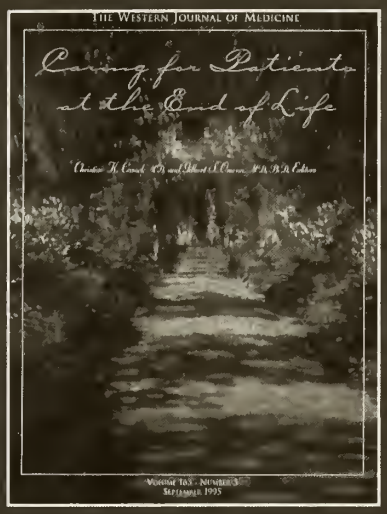

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(Continued from Page 270)

326 **Relations**

NATHANIEL H. ROBIN, MD

From the Department of Genetics and Pediatrics, Case Western Reserve University School of Medicine, and the Center for Human Genetics, University Hospitals of Cleveland, Ohio.

OTHER FEATURES

267 **Coming in the December Issue of WJM**

269 **WJM Subscription Information**

271 **WJM Special Issues**

272 **Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming**

277 **Classified CME Advertising**

331 **Classified Advertising Information**

328 **Classified Advertising**

332 **Western State Medical Associations' Meetings**

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

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March 13–15—**7th Annual Symposium on Coronary Stenting.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs–Sat. Contact: Laurel Steigerwald, Conference Coordinator, Dept. Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, 92037. (619) 554-8556.

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January 20-22—**Opthalmology and ENT for the Primary Care Physician.** CMEA at Hyatt Regency, La Jolla. Mon-Wed. 20 hrs. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego, 92198. (800) 993-2632 or (619) 674-5200.

January 31-February 2—**Primary Care Dermatology.** UCSD at San Diego Hilton Beach and Tennis Resort. Fri-Sun. Contact: UCSD. (619) 534-3940.

January 31-February 1-2—**35th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital, Los Angeles, at Sheraton Universal Hotel, Universal City. 15 hrs. $295. Contact: David J. Stewart, MB, Program Director, Pediatric Anesthesiology Conference, Children's Hospital Los Angeles, PO Box 54700, Los Angeles, CA 90054. (213) 669-2262.

February 7-10—**CAFP 49th Annual Scientific Assembly.** CAFP at Hyatt Regency, San Francisco, Fri-Mon. $275-$385. Contact: Clark W. Franklin, CAFP, 114 Sansome St., Ste. 1305, San Francisco, CA 94104-3824. (415) 394-9121.

February 14-16—**Office Gynecology and Women's Health for the Primary Care Physician.** CMEA at Hyatt Islandia, San Diego, Fri.-Sun. 20 hrs. $475. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego 92198. (800) 993-2632 or (619) 674-5200.

February 16-21—**12th Annual Primary Care Medicine: Concepts and Controversies.** UCSF at Squaw Creek, CA 20 hrs. $625. Contact: UCSF.

February 17-20—**Clinical Hematology and Oncology: 1997.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Scripps, (619) 554-8556.

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CONTINUING MEDICAL EDUCATION

February 19-23—**The Practicing Physician's Approach to the Difficult Headache Patient.** Dannemiller Memorial Educational Foundation at Marriott's Las Palmas Resort and Country Club, Rancho Mirage. Wed-Sun. 22 hrs. $345. Contact: Meeting Coordinator, Diamond Headache Clinic Research and Educational Foundation, 467 West Deming Place, Chicago, IL, 60614. (312) 388-6363.

February 21—**Modern Approaches to Allergic Diseases for the Primary Care Physician.** UCSF at Moscone Center, San Francisco. Fri. 6.75 hrs. $125. Contact: UCSF.

March 6-8—**Contraceptive Technology Conference.** Contemporary Forums at Fairmont Hotel, San Francisco. Thurs-Sat. 16 hrs. $425. Contact: Contemporary Forums, 11900 Silvergate Drive, Dept 265, Dublin, CA, 94568. (510) 828-7100.

March 20—**Diabetes Update.** UCSF at Holiday Inn, San Francisco. 7.5 hrs. $185. Contact: UCSF.

March 21-22—**Advances in Endocrinology and Metabolism.** UCSF at Holiday Inn, San Francisco. Fri-Sat. 13 hrs. $295. Contact: UCSF.

March 26-28—**Annual Review in Family Medicine.** UCSF at Stanford Court Hotel, San Francisco. Wed-Fri. 16 hrs. $375. Contact: Program Coordinator, Dept. Family and Community Medicine, 500 Parnassus Ave, MU-3E, San Francisco, CA 94143-0900. (415) 476-5250.

April 9-13—**Annual Scientific Program and Postgraduate Course in Fertility.** Pacific Coast Fertility Society at Rennaissance Esmeralda Resort, Indian Wells. Wed-Sun. 19 hrs. Contact: Director of Medical Education or Susan Reddy Butler, Pacific Coast Fertility Society, PO Box 1656, La Mirada, CA, 90637-1656. (310) 947-7068.

April 14-15—**Born Too Soon: Multidisciplinary Strategies for Prevention of Preterm Birth.** Contemporary Forums at Marriott Hotel, Oakland. Mon-Tues. 13 hrs. $375. Contact: Contemporary Forums, 1900 Silvergate Dr., Dept. 280, Dublin, CA, 94568. (510) 828-7100, ext. 0.

April 17-20—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Continuing Medical Education Associates at San Diego Hilton Beach and Tennis Resort. Thurs-Sun. 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego 92198. (800) 993-2632.

May 14–17—**Wound Management Workshop for Primary Care.** UCSD at La Jolla Marriott, San Diego. Wed–Sat. 15 hrs. $475. Contact: UCSD.

May 16–20—**Primary Care Essentials.** Continuing Medical Education Associates at Grand Hyatt on Union Square, San Francisco. Fri–Tues. 32 hrs. $750. Contact: Jacqueline Shiller, CMEA, PO Box 270469, San Diego, 92198 (800) 993-2632.

INFECTIOUS DISEASE

February 6-8, 1997—**Epidemiology and Prevention of Infectious Diseases.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

INTERNAL MEDICINE

February 12-14, 1997—**Recent Adventures in Neurology.** UCSF at Hyatt Regency Hotel, San Francisco. Wed-Fri. 15 hrs. Contact: UCSF.

February 15-20—**22nd Annual Postgraduate Topics & Advances in Internal Medicine.** UCSD at Hyatt Regency, San Diego. Sat-Thurs. 52 hrs. $1365. Contact: UCSD.

February 17-20—**Clinical Hematology and Oncology: 1997.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Scripps, (619) 554-8556.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

March 21-27—**Internal Medicine 1997.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Fri-Thurs. 45 hrs. $795. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

April 5—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Sat. 6 hrs. Contact: Laurel Steigerwald, Conference Coordinator, Dept. Academic Afairs, 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, 92037. (619) 554-8556.

NEPHROLOGY

February 6-8, 1997—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Hotel del Coronado, San Diego. Thurs-Sat. 17 hrs. $395. Contact: UCSD.

NEUROLOGY

January 17–19, 1997—**Advances in the Diagnosis and Clinical Practice in the Neurosciences.** San Diego Hilton Beach and Tennis Resort, San Diego. Fri.–Sun. 7 hrs. Contact: California Association of Neurological Surgeons, (916) 443-0236.

ONCOLOGY

February 17-20, 1997—**Clinical Hematology and Oncology: 1997.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Scripps, (619) 554-8556.

February 20-22, 1997—**Molecular Advances in Cancer Epidemiology and Prevention.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

OTOLARYNGOLOGY

January 4-8, 1997—**Temporal Bone Surgical Dissection Course.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, 2100 W Third St, Los Angeles 90057. (213) 483-4431, ext 7079.

February 1-5—**Temporal Bone Surgical Dissection Course.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs. $1,300. Contact: House Ear Institute, (213) 483-4431, ext 7079.

March 15-19—**1996-1997 Temporal Bone Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat-Wed. 48 hrs. $1300. Contact: Antonio de la Cruz, MD, Director of Educaiton, House Ear Institute, 2100 W Third St, Los Angeles, CA 90057. (213) 483-4431, ext 7079.

April 12-16—**1996-1997 Temporal Bone Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat-Wed. 48 hrs. $1300. Contact: Antonio de la Cruz, MD, Director of Educaiton, House Ear Institute, 2100 W Third St, Los Angeles, CA 90057. (213) 483-4431, ext 7079.

May 3–7—**1996-1997 Temporal Bone Survival Dissection Courses.** House Ear Institute at Los Angeles. Sat–Wed. 48 hrs. $1,300. Contact: The House Ear Institute, Antonio De la Cruz, MD, Director of Education, 2100 W. Third St., Los Angeles, 90057. (213) 483-4431.

PEDIATRICS

January 15-18, 1997—**San Diego Cerebral Palsy Symposium.** Children's Hospital at San Diego Marriott Mission Valley. Wed-Sat. 21.5 hrs, $450-$495. Contact: Continuing Medical Education, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

January 27-31— **San Diego Conference on Responding to Child Maltreatment.** Children's Hospital at Town and Country Hotel, San Diego. Mon-Fri. 30.5 hrs, $435. Contact: Registration Coordinator, Center for Child Protection, 3020 Children's Way (MC5016), San Diego 92123. (916) 495-4940.

January 31-February 2—**35th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Los Angeles at Sheraton Universal Hotel, Universal City. 15 hrs. $295. Contact: David J. Stewart, MB, Program Dir, Pediatric Anesthesiology Conf., Children's Hospital Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

February 1—**Update in Behavioral/Developmental Pediatrics.** UCSF at UCSF Campus. Sat. Contact: UCSF.

February 17–20—**Clinical Hematology and Oncology.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon–Thurs. 24 hrs. Contact: Laurel Steigerwald, Conference Coordinator, Dept. Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, 92037. (619) 554-8556.

February 28-March 2—**Current Concepts in Pediatric Medicine—10th Anniversary.** Children's Hospital and Health Center at San Diego Hilton Beach and Tennis Resort. Fri-Sun. 16 hrs. $365. Contact: Children's Hospital, CME, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

April 4-5—**Pediatric Dermatology for the Practitioner.** Children's Hospital at Hyatt Islandia Mission Bay, San Diego. Fri-Sat. 12 hrs. $245. Contact: CME Office–5021, 3020 Children's Way, San Diego, CA, 92123. (619) 576-4072.

April 4–6—**Nelson Butters' West Coast Neuropsychology Conference: New Neuropsychological Tests for School-Aged Children.** UCSD at US Grant Hotel, San Diego. Fri–Sun. 15.5 hrs. $325. Contact: Cass Jones, Professional Conference Management, Inc. 7916 Convoy Court, San Diego, 92111. (619) 565-9921.

May 15–17—**30th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs–Sat. 15.5 hrs. $375. Contact: UCSF.

PLASTIC SURGERY

March 20–22, 1997—**9th Annual Symposium on Aesthetic Surgery.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 18 hrs. $950. Contact: UCSF.

PSYCHIATRY AND NEUROLOGY

February 12-14, 1997—**Recent Adventures in Neurology.** UCSF at Hyatt Regency Hotel, San Francisco. Wed.-Fri. 15 hrs. Contact: UCSF.

April 3-6—**Nelson Butler's West Coast Psychiatry Conference.** UCSD at US Grant Hotel, San Diego. Thurs-Sun. 15 hrs. $325. Contact: UCSD.

RADIOLOGY

January 26-February 2, 1997—**Multi Specialty Radiology Courses: Neuroradiology, Angiographic, Interventional, Chest, Ultrasound, and Bone.** UCSD at Hotel del Coronado, San Diego. Sun-Sun. Various hours. $975. Contact: Ryals & Associates, Inc, PO Box 1925 Roswell, GA, 30077-1925. (770) 641-9773.

March 29—**10th Annual Spring Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 6.25 hrs. $145. Contact: UCSD.

March 30-April 4—**17th Annual San Diego Residents Radiology Review.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 41 hrs. $695. Contact: UCSD.

SURGERY

January 4-8, 1997—**Temporal Bone Surgical Dissection Course.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs. $1,300. Contact: House Ear Institute, 2100 W Third St, Los Angeles 90057. (213) 483-4431, ext 7079.

GENERAL/MULTIDISCIPLINARY

December 12-14—**Diagnosis and Treatment of Back Pain—The Next Level.** St Mary's Hospital at Stanford Court Hotel, San Francisco. Thurs-Sat. Contact: Aubrey A. Swartz, MD, American Back Society, St Joseph's Professional Center, 2647 E 14th St, Ste 401, Oakland 94601. (510) 536-9929.

January 8, 1997—**Pre-ACLS Workshop.** AHA at San Leandro. Wed. 6 hrs. $50-$70. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro, CA 94577. (510) 632-6135.

January 17, 18, 19—**ACLS Renewal/Provider.** AHA at San Leandro. Fri-Sun. 6 hrs. $100. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro, CA 94577. (510) 632-6135.

January 22–25—**Medicine Meets VR—Global Healthcare Grid: Transformation of Medicine Through Communication.** UCSD at San Diego Marriott Hotel & Resort. Wed–Sat. Contact: Alligned Management Associates,

(619) 749-2498.

February 1-2—**PALS Instructor.** AHA at San Leandro. Sat-Sun. 16 hrs. $170. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro, CA 94577. (510) 632-6135.

February 8-9—**ACLS Instructor.** AHA at San Leandro. Sat-Sun. 16 hrs. $195. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro, CA 94577. (510) 632-6135.

April 24-25—**New Frontiers in Alzheimer's Disease.** UCSD at San Diego Hilton. Thurs-Fri. 16 hrs. $210.

May 13—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at Scripps Clinic, La Jolla. Sat. 7 hrs. Contact: Laurel Steigerwald, Conference Coordinator, Dept. Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, 92037. (619) 554-8556.

HOME STUDY/SELF-ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

January 16–19, 1997—**Anxiety Disorders: Colorado Psychiatric Association Annual Meeting.** Vail. Thurs–Sun. Contact: Laura Michaels, 759-6045.

February 16–21—**23rd Annual Vail Obstetrics & Gynecology Conference.** University of Colorado. Vail. Sun–Sun. Contact: Linda Woodstock, 372-9026.

February 23–26—**Team Approach to Pediatric Cardiac Disease.** The Children's Hospital. Vail Cascade Hotel and Club. Sun–Wed. Contact: Alice L. Kay, 861-6123.

March 1–7—**CRASH 97 Colorado Review of Anesthesia and Ski Holiday.** University of Colorado Dept. of Anesthesiology. Vail. Sat–Fri. Contact: Phyllis Tuller, 372-6901.

March 15–19—**Thoracic Transplantation 1997: An International Update.** Division of Cardiothoracic Surgery, University of Colorado. Marriott's Mountain Resort, Vail. Sat–Wed. Contact: U of Colo, 270-3065.

March 15–21—**Reconstructive Surgery of the Hip and Knee.** University of Colorado, Aspen. Sat–Fri. Contact: Joan Bauer (800) 882-9153.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

This listing of continuing medical education programs in Idaho is compiled by the Ada County Medical Society. To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930.

Brochures, course information, and registration forms are available from the contact person or organization.

February 14–16, 1997—**ACMS 28th Annual Medical Winter Clinics.** Shore Lodge Inn, McCall, Idaho. Fri-Mon. 9 hrs. Contact: Judy Barningham (208) 336-2930 or Marie Chester (208) 381-2135.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

December 11-14—**The Veterans Caucus 5th Annual Topics in the Tropics.** Sol Melia Beach and Spa Resort, Cancún, Mexico. Wed.-Sat. Contact: Sharon Hanley, RMP, Conference Coordinator, Geisinger Clinic, 100 N. Academy Ave., Danville, PA 17822-1350.

January 11-12, 1997—**15th Albuquerque Family Practice Seminar.** Albuquerque Hilton. Sat.-Sun. Contact: Ann Woodrow, Albuquerque Academy of Family Physicians, 2309 Renard SE, #208, Albuquerque, NM 87106. (505) 243-4560.

February 28-March 1—**25th Annual New Mexico Thoracic Society Lung Disease Symposium.** Taos. Fri-Sat. Contact: Billie Dytzel, 216 Truman NE, Albuquerque 87108. (505) 265-0732; (800) 221-LUNG. FAX (505) 260-1739.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

February 5-9—**3rd Annual Brigham & Women's Utah Therapeutic GI Endoscopy Course 1996: Problems and Solutions.** Park City. Contact: UUSM.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS:	Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

December 12–14—**Annual Meeting: Washington State Chapter American College of Physicians**. Seattle. Thur.-Sat. Contact: U/W CME (206) 543-1050.

December 12–14—**The 12th Annual Infectious Disease Conference**. Seattle. Thur.-Sat. Contact: PNCEI (360) 653-4543.

December 13—**Alternative Medicine 1996**. Bellevue. Fri. Contact: Group Health Cooperative of Puget Sound (206) 326-3441.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

OTHER CME OPPORTUNITIES

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE. May 9–16, 1997—**56th Annual American Occupational Health Conference**. Orange County Convention Center, Orlando, Fla. Fri.–Fri. Contact: ACOEM, 55 W. Seegers Rd., Arlington Heights, Ill 60005. (847) 228-6850, FAX (847) 228-1856.

THE CENTER FOR BIO-MEDICAL COMMUNICATION, INC. March 7–9—**Management of the HIV-Infected Patient—A Practical Approach for the Primary Care Practitioner**. Crowne Plaza Manhattan, New York City, NY. Fri.–Sun. Contact: Center for Bio-Medical Communication, Inc. (201) 385-8080, FAX (201) 385-5650.

CREIGHTON UNIVERSITY SCHOOL OF MEDICINE. July 9–11, 1997—**14th Annual Scientific Session of the American Association of Clinical Anatomists**. Honolulu. Wed–Fri. Contact: Sally C. O'Neill, PhD, Associate Dean, Creighton University CME Division, 601 North 30th St., Suite 2130, Omaha, NE 68131. (800) 548-CMED or (402) 280-1830.

CREIGHTON UNIVERSITY SCHOOL OF MEDICINE, July 12, 1997—**Clinical Anatomy of the Basic Physical Examination**. Honolulu. Sat. Contact: Sally C. O'Neill, PhD, Associate Dean, Creighton University CME Division, 601 North 30th St., Suite 2130, Omaha, NE 68131. (800) 548-CMED or (402) 280-1830.

INSTITUTE FOR JEWISH MEDICAL ETHICS. February 14–17 1997—**8th Annual International Conference on Jewish Medical Ethics**. San Francisco. Fri–Mon. 27 units CME credit. Jointly sponsored by the Institute for Jewish Medical Ethics of San Francisco and Stanford University School of Medicine. Contact: IJME, (800) 258-4427.

NATIONAL MANAGED HEALTH CARE CONGRESS. January 28–31, 1997—**6th Annual West Managed Health Care Congress**. Palm Springs, Calif. Contact: NMHCC. (617) 505-8000, FAX (617) 270-600.

PHYSICIANS FOR A VIOLENCE-FREE SOCIETY. February 7–8—**4th Annual Conference: "Alcohol: Fuel for Family Violence?"** Hyatt at Fisherman's Wharf, San Francisco, Calif. Contact: JoAn Dwyer, PO Box 35528, Dallas, TX 75235-0528. (214) 590-8807, FAX (214) 590-4079.

UNIVERSITY OF NEBRASKA. February 14, 1997—**Cardiovascular Research Symposium**. Omaha. Fri. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. March 2–7—**17th Annual Keystone Conference: Review of Head and Neck Medicine for the Primary Care Physician**. Omaha. Sun–Fri. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

CONTINUING MEDICAL EDUCATION

UNIVERSITY OF NEBRASKA. March 10–21—**Family Practice Review: Skills for the 21st Century**. Omaha. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. March 20–22—**National Association of Medical Direction of Respiratory Care**. Omaha. Thu–Sat. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE. March 21–22, 1997—**Integrated Care of the Thoracic Surgery Patient—A Seminar for Allied Health Professionals**. St. Louis, Mo. Fri.–Sat. Contact: Office of Continuing Medical Education, Washington University School of Medicine, Campus Box 8063, 660 South Euclid Ave., St. Louis, Mo 63110-1093. (800) 325-9862, FAX (314) 362-1087.

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE. April 4–5—**Clinical Pulmonary Update**. St. Louis, Mo. Fri.–Sat. Contact: Office of Continuing Medical Education, Washington University School of Medicine, Campus Box 8063, 660 South Euclid Ave., St. Louis, Mo 63110-1093. (800) 325-9862, FAX (314) 362-1087.

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE. April 10–12—**Refresher Course & Update in General Surgery**. The Ritz-Carlton Hotel, St. Louis, Mo. Thu.–Sat. Contact: Office of Continuing Medical Education, Washington University School of Medicine, Campus Box 8063, 660 South Euclid Ave., St. Louis, Mo 63110-1093. (800) 325-9862, FAX (314) 362-1087.

NOTICE

State Associations should send their CME listings for publication to:

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Articles

Sir William Macewen's Visit to California as the First Lane Medical Lecturer

A Centennial Celebration

THOMAS M. KELLER, MD, MPH, *Oakland, California*

1996 marked the centennial anniversary of the 1896 visit to California of William Macewen, MD, Regius Professor of Surgery of the University of Glasgow, Scotland, to give the first Lane Medical Lectures. I describe the origins of this historic lecture series and include photographic records. The progress and development of modern California medicine have been greatly influenced by the personalities who initiated and nurtured this lecture series.

(Keller TM: Sir William Macewen's visit to California as the first Lane Medical Lecturer—A centennial celebration. West J Med 1996; 165:279–282)

Bring me men to match my mountains . . .

SAM FOSS
The Coming American[1]

As the 19th century drew to a close, California symbolized for many Americans a century of spectacular achievements. The discovery of gold at Sutter's Mill in 1848 spurred the immigration of the first wave of adventurers to the area, bringing statehood in 1850, while the completion of the transcontinental railroad in 1869 over the Sierra Nevadas resulted in a rapid increase in population and commerce from the East.[2,3] When Levi Cooper Lane, MD, foremost surgeon of the Pacific Coast, founded Cooper Medical College in 1882, the state's growing sophistication became clear.[4]

National acknowledgment of the West Coast's importance in health care came in 1895 with the election to the presidency of the American Medical Association of Richard Beverly Cole, MD, San Francisco obstetrician and University of California professor.[5] Elated by the new medical prominence of California, by his school's accomplishments, and by the opening of his new Lane Hospital in San Francisco early in 1896, Professor Lane decided to endow a lecture series to commemorate these events. He hoped that by bringing the medical profession of the Far West into closer contact with the more progressive medical minds in the East and in Europe, the lectures would foster an intellectual culture and encourage scientific research.[6]

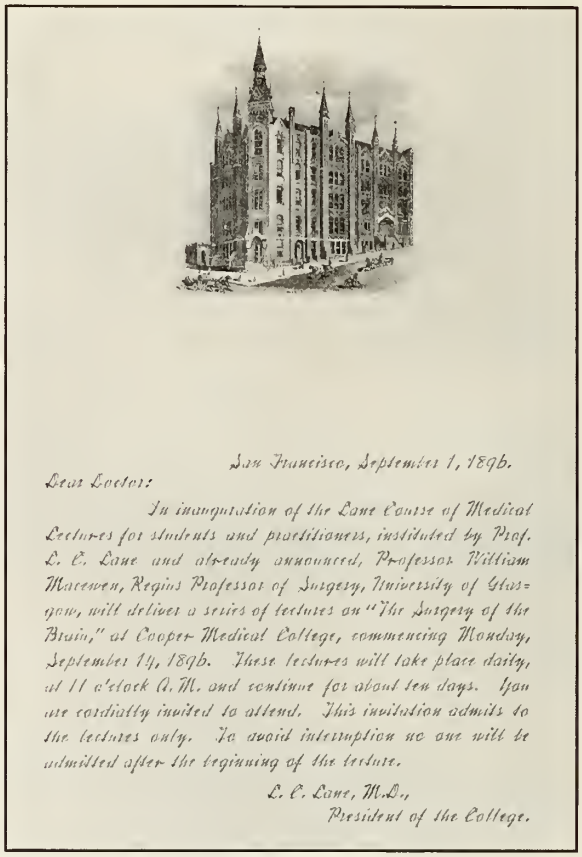
In the spring of 1895, Lane sent for Adolph Barkan, MD, Professor of Ophthalmology and Otology at Cooper Medical College, who was about to leave for a European tour, and told him of his plan to establish the lecture series. Discussing the choice of an inaugural speaker, the two physicians decided almost immediately on Professor William Macewen of the University of Glasgow, Scotland. Lane asked Barkan to deliver his invitation personally.

It had not been difficult to select Macewen, who, at the pinnacle of his career, was one of Europe's leading surgeons. Appointed Regius Professor in 1892, the 48-year-old Scottish surgeon had either pioneered or formulated major advances in aseptic surgery, tracheal intubation, herniorrhaphy, and orthopedics.[7] He performed the first complete pneumonectomy for tuberculosis immediately before Barkan's visit in April of 1895.

Macewen's accomplishments in cerebral surgery and the surgical treatment of mastoiditis were also well known. Barkan, an otologist, and Lane, the first surgeon in America to relieve a case of microcephalus by craniectomy and author of a new text on head and neck surgery, were confident that they had chosen wisely.[8,9]

Cabling Macewen in Glasgow, Lane extended his invitation and arranged for Barkan and Professor Macewen to meet in London on the evening before Macewen's address to the British Medical Association on the subject of brain surgery.[10] Macewen became enthralled with the idea of visiting the American West and of seeing California, a land of promise, hope, and dreams for many Europeans. He declined the honorarium suggested by Lane of $2,000—a princely sum in 1896, about equal to the annual salaries of the noted University of California professors Joseph LeConte, MD, and Eugene Hilgard, MD, and twice the salary of the first full-time Cooper College professor appointed in 1898, William Ophuls, MD, Professor of Pathology[11]—remarking, "The fee does not tempt me, but I like the idea."[6(p603)]

From the Pacific Neurosciences Institute, Division of Surgery, University of California, Davis (UCD)–East Bay, Oakland.
Reprint requests to Thomas M. Keller, MD, MPH, Pacific Neurosciences Institute, Div of Surgery, UCD–East Bay, 1411 East 31st St, Oakland, CA 94602.



San Francisco, September 1, 1896.

Dear Doctor:

In inauguration of the Lane Course of Medical Lectures for students and practitioners, instituted by Prof. L. C. Lane and already announced, Professor William Macewen, Regius Professor of Surgery, University of Glasgow, will deliver a series of lectures on "The Surgery of the Brain," at Cooper Medical College, commencing Monday, September 14, 1896. These lectures will take place daily, at 11 o'clock A. M. and continue for about ten days. You are cordially invited to attend. This invitation admits to the lectures only. To avoid interruption no one will be admitted after the beginning of the lecture.

L. C. Lane, M.D.,
President of the College.

Figure 1.—A formal invitation was sent to physicians to attend the first Lane Medical Lecture, with an engraving of Cooper Medical College.

Before Macewen could accept the offer, however, he had to secure approval from the royal family to absent himself from his role as surgeon to the King of England. Having settled this issue, Macewen formally accepted the invitation to deliver the first course in the Lane Medical Lectures in San Francisco, California, from September 14 to 25, 1896 (Figure 1).

First Lane Medical Lecture

Macewen embarked for San Francisco in early September of 1896, traveling across Canada on the newly inaugurated Canada–Pacific railroad to Oakland, California, where he was met by Cooper College professors (Figure 2). They took Macewen on a brief tour, welcoming him to the San Francisco Bay Area and the University of California. There he met with Professor William Ritter of the Department of Zoology, who was studying a topic of great interest to Macewen—changes in the bronchial epithelium of the newt as it changed its habitat from land to water.[12]

In his lectures, Macewen described the contemporary clinical diagnosis and operative treatment of brain trauma, brain abscess, and cerebral tumors, leading the audience on a didactic tour de force of work he pioneered in conjunction with Paul Broca, MD, William Ferrier, MD, J. Hughlings Jackson, MD, and Jean Charcot, MD.[13–16] He showed many plates from his *Topographical Atlas of the Brain*.[17] Transcripts of the complete lectures were eventually published in *Occidental Medical Times*.[18]

An estimated 700 or more physicians and students of Cooper Medical College crowded the hall for each of the lectures. Lane, who realized the historic significance of the occasion for the student body, arranged for each student to have a card signed by Macewen verifying his or her attendance. Macewen also generously performed two operations for the benefit of the students, an osteotomy for genu valgum and a radical mastoidectomy with Drs Stillman and Rixford assisting.

During a sumptuous banquet given in Macewen's honor, Edward Robeson Taylor, MD, Cooper College's Vice-President and eclectic lawyer-physician-poet, read an ode to Macewen, extolling his feats of cerebral surgery[19,20]:

> Even cranial walls oppose in vain:
> For breaking through,
> You seize the demons of the brain,
> By faultless clew,
> And set their tortured victims free,
> That life and joy again may be.

Reluctant to be photographed, Macewen nevertheless agreed to pose with Drs Lane, Barkan, Hirschfelder (Cooper professor responsible for America's first surgical treatment of primary brain tumor),[21] and Stillman

Figure 2.—Professor William Macewen was photographed on September 20, 1896, during a tour of the San Francisco Bay Area. Adolph Barkan, MD, was driving the buggy and Thomas Stillman, MD, was seated on the horse.

(responsible for an early 1894 series of laminectomies in California)[22] (Figure 3).

To express the school's gratitude, Lane chose Ray Lyman Wilbur, a young medical student who later became Dean of the Stanford Medical School, President of Stanford University Medical School, President of the American Medical Association, Secretary of the Interior under President Herbert Hoover, and one of the great men in American medicine.[23] As an aside, his son, Dwight Wilbur, MD, carried on this legacy of service as Editor of *The Western Journal of Medicine* from 1946 to 1966 and, like his father, was President of the American Medical Association in 1967.[24]

On October 2, 1896, the Lane Hospital's Board of Directors, honoring Professor Macewen for the success of the first Lane Medical Lectures, noted that Lane had personally commended him for his gracious personality and his inspiration to California's medical profession.

Aftermath

In subsequent Lane lectures, distinguished names in medicine and surgery continued in Macewen's footsteps. Among them were Sir Thomas Allbutt, Regius Professor of the University of Cambridge, England; Nicolas Senn, MD, Professor of Surgery, Rush Medical College (Chicago, Illinois); William Welch, MD, Professor of Pathology, Johns Hopkins University School of Medicine (Baltimore, Maryland); Reginald Fitz, MD, Professor of Medicine, Harvard Medical School (Boston, Massachusetts); and Simon Flexner, MD, Director of Laboratories, Institute for Medical Research (New York City). For many years, Macewen assisted Lane in appointing lecturers. As evidence of the care with which Lane selected his speakers and the quality of his advice, most of the British lecturers chosen subsequently received knighthood for their service to medical science. It was fitting that in 1947, the golden anniversary of the Lane Lectures initiated by Professor Macewen, another great surgical neurologist, Wilder Penfield, MD, Director of the Montreal Neurological Institute of McGill University Faculty of Medicine, gave the lecture, "Physiological Observations of the Cerebral Cortex of Man." The Lane Medical Lectures continue to draw eminent medical scientists from around the world to teach and inspire.[25]

Dr Levi Cooper Lane died on February 18, 1902. Appropriately, when Cooper Medical College became part of Stanford University in 1909, Lane, so intimate with the heritage, traditions, and languages of the Old World, and Leland Stanford, whose railroad more closely bound the Old World and California, posthumously shared credit for this legacy.

The story has a brief postscript. While on his journey in 1923 as the British Medical Association's "ambassador" to the Australasian Medical Association, Macewen, now on his second visit to California, was

Seated: Dr. L. C. Lane facing Professor McEwen, the first Lane Lecturer (holding skull). *Standing*: Dr. Stillman behind Professor McEwen, Dr. Hirschfelder behind Dr. Lane, Dr. Adolph Barkan between.

Figure 3.—This group photograph was taken of L. C. Lane, MD, Professor William Macewen, and Cooper Medical College physicians.

taken on a tour of Sequoia National Park by Dr Emmet Rixford. After spending the day wandering among the giant trees, the old surgeon turned to his guide and said, "Rixford, this is the greatest thing I have ever seen."[26] Thus was paid any lingering debt of the California medical profession to Macewen for his magnificent lectures 27 years earlier. A year later, on March 22, 1924, Macewen died of cardiac failure complicating a severe bout of pneumonia.[27]

Acknowledgment

The invaluable assistance in the preparation of this manuscript by Heidi Heileman, Archivist of the Lane Medical Library, Stanford University Medical School, and Robin Chandler, Special Collections Librarian of the University of California, San Francisco, Medical Library is greatly appreciated.

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Articles

Serious Mushroom Poisonings in California Requiring Hospital Admission, 1990 Through 1994

JEFFREY JACOBS, MD, MPH; JULIE VON BEHREN, MPH; *and* RICHARD KREUTZER, MD, *Emeryville, California*

Hunting and consuming wild mushrooms is an increasingly popular avocation, as well as a means of subsistence for certain groups in the United States. Consuming wild mushrooms is relatively safe for persons with the necessary expert knowledge. Each year, however, tragic deaths or illnesses occur when unsuspecting persons ingest toxic mushrooms. We conjectured that there may be vulnerable subgroups that should be targeted for public service announcements and education about mushrooms. Therefore, we reviewed California's hospital discharge database from 1990 through 1994 to ascertain demographic characteristics and outcomes of "serious" mushroom exposures requiring a hospital admission. Children younger than 5 years have a higher rate of hospital admission for "serious" poisonings. Therefore, parents should be reminded of the need for supervising children in areas with wild mushrooms. We did not find evidence that poisoning rates differed significantly between ethnic or racial groups, but this finding may be limited by a failure of these groups to seek care after becoming ill. We discuss briefly the symptoms and treatment of cases of possibly lethal ingestion of amatoxin-containing species of mushrooms.

(Jacobs J, Von Behren J, Kreutzer R: Serious mushroom poisonings in California requiring hospital admission, 1990 through 1994. West J Med 1996; 165:283–288)

In early February 1996, five northern Californians ingested poisonous mushrooms, resulting in one death and a lifesaving liver transplantation in another. In the fatal case, a migrant farm laborer became ill after eating mushrooms he picked from a field. He died three days later, never having sought medical attention. In the other case, a family picked wild mushrooms with a friend, who assured them that the mushrooms were safe to eat. Six to ten hours later, the family members—a woman, her two sons, and a daughter—began vomiting and having profuse watery diarrhea and crampy abdominal pains, and they sought medical attention. Over the next several days, three of the family members' liver function deteriorated but then improved. The young girl's health continued to deteriorate, and a partial liver transplantation was done. Her health and liver function rebounded after the procedure, allowing for the removal of the temporary transplant.

Background

These cases illustrate the possible risk associated with consuming wild mushrooms without appropriate expert knowledge. Most mushrooms are not poisonous. Of the 5,000 known species of mushrooms, fewer than 100 are poisonous to humans.[1,2]* The origin of the word mushroom dates back to early Greek times and is best translated to the word "mucus."[2] Mushrooms were thought to have arisen from slimy, mucoid matter and were believed linked to frogs and toads, hence the name "toadstool." Whereas poisonous properties of wild mushrooms have been recognized since ancient times, most people consuming wild mushrooms have lived to tell about it. Euripides is credited with the earliest report of mushroom poisoning in 430 BC when, on a trip to Icarus, he recorded the fatal poisoning of a woman and her three children. Famous victims of mushroom poisoning include Pope Clement II, the widow of Tsar Alexis, and Charles VI of France.[2]

Today wild mushrooms are greatly prized as a culinary treat, and the popularity of mushroom hunting is growing throughout the world. Numerous guidebooks are available, and expert knowledge from mycologic clubs and societies enables novice collectors to forage with increased awareness of the dangers of toxic mushrooms. Despite this increased awareness, however, seri-

*See also the editorial by C.W. Pinson, MD, MBA, and Anne L. Bradley, MD, "A Primer for Clinicians on Mushroom Poisoning in the West," on pages 318–319 of this issue.

From the California Department of Health Services, Environmental Health Investigations Branch, Emeryville.
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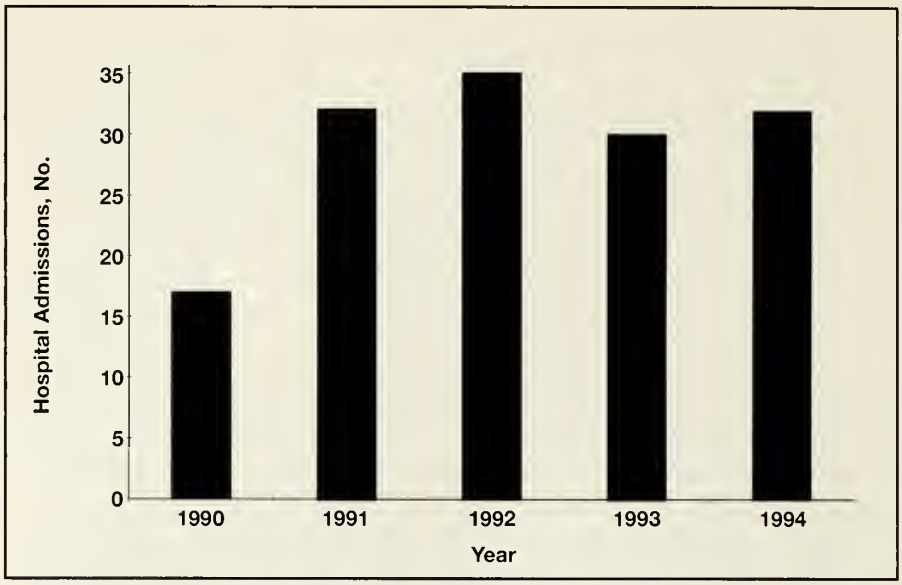

Figure 1.—The graph shows the number of admissions to California hospitals for mushroom poisoning by year during 1990 through 1994 (n = 146). They averaged 29.2 per year during this period.

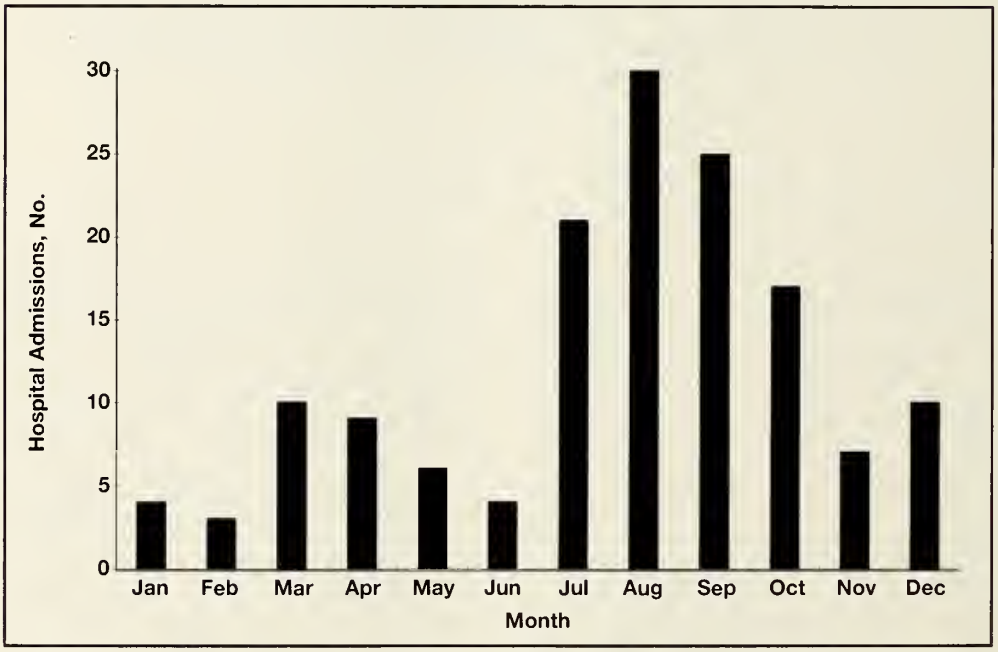

Figure 2.—The number of admissions to California hospitals for mushroom poisoning for 1990 through 1994 (n = 146) is shown by month. Admissions for mushroom poisoning were more common in summer and early fall, peaking in August.

ous poisoning episodes continue to occur. This problem is especially common in Europe, where wild mushrooms are more widely collected and several hundred deaths occur annually.[1,3]

A number of conditions are associated with mushroom poisoning. Many adults seem unaware of the risks of eating wild mushrooms. Inexperienced mushroom hunters may mistake the identity of a mushroom. Immigrants may come from areas where only edible look-alikes exist. Unsupervised infants, persons looking for hallucinogenic materials, and families who are told by "authorities" that the mushrooms are edible may be poisoned as well.[4]

Cases and Methods

We examined California's cases of "serious" mushroom poisonings requiring admission to a hospital. We elected to use the California Office of Statewide Health Planning and Development (OSHPD) Discharge Database.[5] This database provided us with pertinent demo-

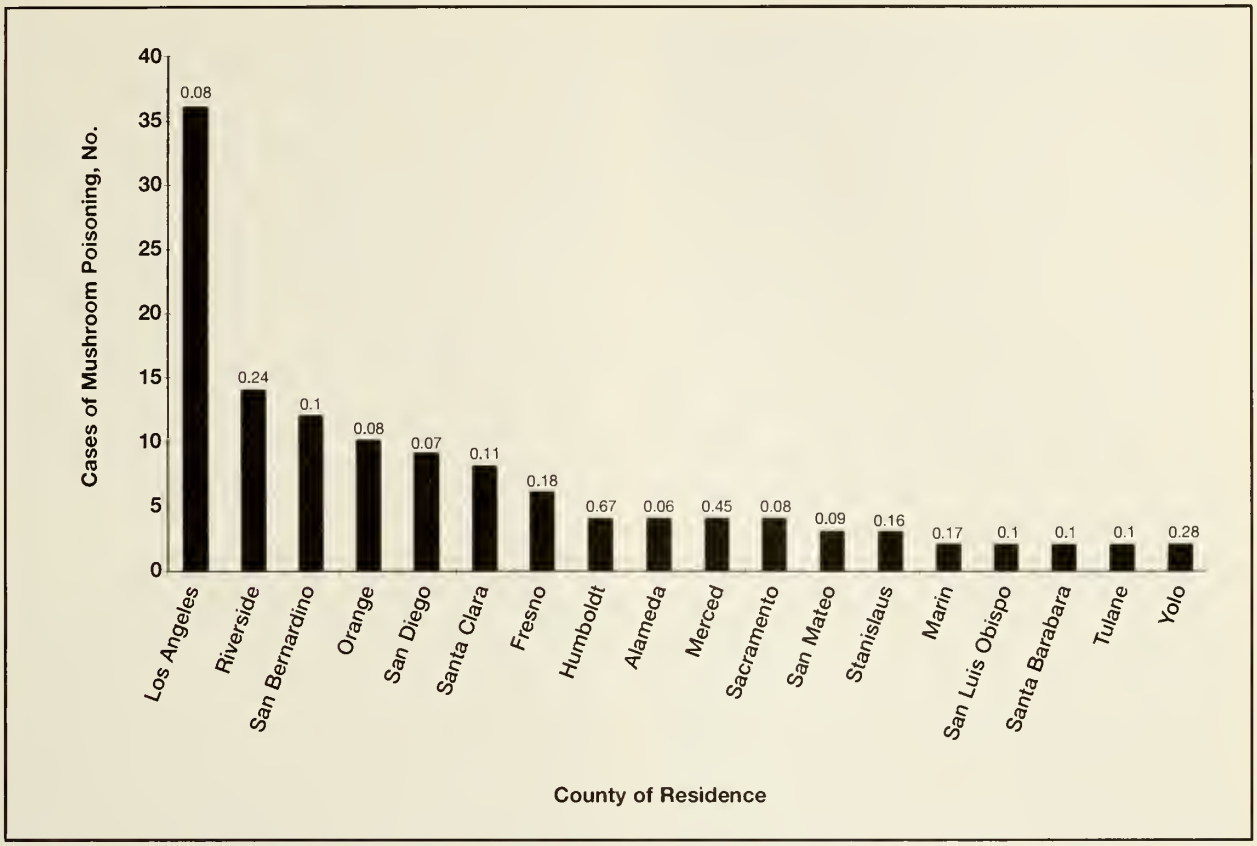

Figure 3.—The number of admissions to California hospitals for mushroom poisoning (rate per 10^5 person-years shown above bars) during 1990 through 1994 (n = 146) is shown by selected counties of residence. The most hospital admissions for mushroom poisoning were among residents of Los Angeles County. When cases were adjusted by population, Humboldt County (northern California) had the highest hospital admission rate in the state, with 0.67 cases per 10^5 person-years.

graphic information on mushroom poisoning victims and the outcome of cases.

The OSHPD Discharge Database contains computerized records for all hospital admissions in California. Cases were selected for the years 1990 through 1994, if the primary E code was listed as mushroom poisoning (*International Classification of Diseases*, 9th revision, code E 865.5),[6] regardless of the actual primary diagnosis code. We obtained demographic information, including the age, race, and sex of each patient. Hospital information included county of residence for each poisoning case and the month, day of week, and year of the admission. Outcome information included the length of hospital stay, the primary procedure done in the hospital, and the disposition of each patient. To check for victims of mushroom poisoning who died before being admitted to a hospital, we searched the California Death Registry[7] for cause by mushroom poisoning (death code 865.5) from 1985 through 1994. We found only four cases, which occurred in March 1985, all in San Diego County. These were not included in our data.

Frequency counts for some of the OSHPD data were standardized into rates by calculating person-years for the population at risk (all Californians). These data were obtained from 1990 census information.[8] Statistical

TABLE 1.—*Demographics of Persons in California With Mushroom Poisoning Requiring Hospital Admission, 1990 Through 1994*

Demagraphic	*Number*	*(%)*	*Rate/10^5 person-yr*
Age, yr			
<5	26	(17.8)	0.22
5 to 18	25	(17.1)	0.09
19 to 44	56	(38.4)	0.08
45 to 64	22	(15.1)	0.09
≥65	17	(11.6)	0.11
Total	146	(100.0)	
Race			
White	87	(59.6)	0.1
Black	7	(4.8)	0.07
Hispanic	37	(25.3)	0.1
Native American	1	(0.7)	- -*
Asian	10	(6.9)	0.07
Unknown	4	(2.7)	- -
Total	146	(100.0)	
Sex			
Male	84	(57.5)	0.10
Female	62	(42.5)	0.08
Total	146	(100.0)	

*Rate not calculated because of small number of cases.

TABLE 2.—*Length of Stay, Principal Procedures Performed, and Disposition for Persons in California With Mushroom Poisoning Requiring Hospital Admission, 1990 Through 1994*

Category	*Patients, Number*	*(%)*
Length of stay, days		
0*	27	(18.5)
1	65	(44.5)
2	28	(19.2)
3	12	(8.2)
4	3	(2.1)
5	4	(2.7)
6	4	(2.7)
7	1	(0.7)
8	1	(0.7)
9	1	(0.7)
Total	146	(100.0)
Principal procedures		
Cardiac monitoring	14	(32.5)
Gastric lavage	15	(34.9)
Other diagnostic tests	11	(25.6)
Peritoneal lavage	3	(7.0)
Total	43	(100.0)
Discharge disposition		
Routine discharge	136	(93.1)
Short-term care	3	(2.1)
Skilled nursing	1	(0.7)
Against medical advice	5	(3.4)
Home health services	1	(0.7)
Deceased	0	(0.0)
Total	146	(100.0)

*No overnight stay.

analysis was performed using the STATA statistical software packages.[9]

Results

There were 146 admissions for mushroom poisoning to California hospitals from 1990 through 1994, averaging more than 29 admissions per year and ranging from 17 in 1990 to 35 in 1992 (Figure 1). We were unable to determine the species of mushroom associated with each case. Most poisoning admissions were in the summer and fall months (Figure 2), peaking during August. The counties with the greatest number of hospital admissions for mushroom poisoning were Los Angeles (36), Riverside (14), San Bernardino (12), Orange (10), San Diego (9), Santa Clara (8), and Fresno (6) (Figure 3). When these county frequencies were divided by person-years, Humboldt County had the highest rate of admissions for mushroom poisoning, with 0.67 cases per 100,000 person-years, followed by Merced (0.45), Yolo (0.28), Riverside (0.24), Fresno (0.18), Marin (0.17), and Stanislaus (0.16).

Demographics for all cases admitted to a hospital for mushroom poisoning are shown in Table 1. The distribution of hospital admissions by age category indicates that children younger than 5 years had the highest rate of admission for poisoning, with 0.22 per 100,000 person-years. Adults aged 65 years or older had the next highest rate (0.11). The distribution of cases by race indicates that non–Hispanic whites had the greatest number of hospital admissions, followed by Hispanics, Asians, African Americans, and Native Americans. Four persons were not classified by race. Males were admitted to a hospital for mushroom poisoning more frequently than females by a ratio of 1.4 to 1.

Once a poisoning victim was admitted to a hospital, the primary procedures performed included gastric lavage, cardiac monitoring, other diagnostic procedures such as lumbar punctures and respiratory monitoring, and peritoneal dialysis (Table 2). No liver transplantations were done for poisoning victims during this time period. The typical length of stay was less than 4 days in more than 88% of the cases. The great majority (93%) of the patients improved and were routinely discharged, 3% left against medical advice, and none died.

Discussion

Hospital admissions for mushroom poisoning in California occur more frequently in the warmer months and reach their peak in August. In general, the typical peak season for wild mushrooms coincides with the rainy season. In California, this is usually from late October through March. The farther north along the West Coast, the season arrives progressively earlier and is compressed; the farther south, it starts correspondingly later and is more erratic.[10(p25)] We are unsure of the reasons behind the discordance between the peak hospital admission rate and peak growth and were unable to review the individual cases to ascertain the offending mushroom. The California admissions peak for mushroom poisoning in summer may, in large part, be due to the mistaken ingestion of poisonous *Agaricus* species (which resemble other edible types), resulting in gastrointestinal symptoms and admission for dehydration.

The location of hospitalizations for mushroom poisoning reflects the great diversity of habitats where poisonous wild mushrooms may be found. More poisonings might be expected in the wetter northern California counties, but drier, more southerly counties such as San Diego and Orange have a substantial number of hospital admissions for poisoning as well. High rates in San Joaquin Valley counties of Fresno and Merced indicate that toxic wild mushrooms can be encountered throughout the state and not just along the coast. In addition, more urban counties like Los Angeles County have large numbers of admissions because they have a large population that may hunt for wild mushrooms. Because wild mushrooms are capable of growing on lawns and median strips, excursions into more rural areas may not be necessary for finding poisonous mushrooms.

Our data suggest that, compared with adults, young children—younger than 5 years—have more than twice the risk of being admitted to a hospital for eating a poisonous mushroom. One scenario may entail an unsupervised or poorly supervised child playing outdoors and eating a mushroom he or she pulls from the ground. In a survey of the American Association of Poison Control

Center's 1989 National Data Collection System, it was found that 81% of reported cases of mushroom exposures occurred in those younger than 6 years.[11] Another explanation may be metabolic differences, with children being more vulnerable to mushroom toxins than adults. In addition, clinicians may be more apt to admit children to a hospital for the intravenous treatment of excessive fluid and electrolyte loss through vomiting and diarrhea, whereas adults are more likely to be discharged with instructions to increase their oral intake of fluids.

Poisonings have been reported to occur when immigrants coming from areas where only edible mushrooms exist encounter a poisonous look-alike in their new community.[4] We had heard this story in reference to Asian communities who forage for wild mushrooms for subsistence. But our data do not reflect an increased prevalence of admissions for mushroom poisoning for any racial group. The lack of an elevation of risk in any ethnic community would seem to lessen the need for increased education targeted toward a specific racial group. This suggestion should be tempered with the understanding that our data may be limited because immigrant groups may also be less likely to seek care, despite becoming ill after eating toxic mushrooms, as the brief report of the farmworker in the initial paragraph illustrates.

The duration of hospital stays was short (<4 days) in most cases, reflecting the generally favorable prognosis after eating toxic mushrooms. Mushrooms produce different types of poisoning—that is, gastrointestinal irritation from unknown toxins; perspiration and lacrimation by muscarine; hallucinations from psilocybin; headache, sweating, and palpitations from coprine; and hepatotoxicity from amatoxin—that are called mycetisms.[2,3] The overwhelming majority of patients with poisonous ingestions have a good prognosis, and the only treatment needed is inducing emesis and supportive care (hydration). The ingestion of mushrooms containing amatoxin (species of *Amanita, Galerina*, and *Lepiota*), however, is the exception to this rule. Of these, the most lethal is *Amanita phalloides*, which has been estimated to cause 90% to 95% of all mushroom poisoning deaths.[1,2] Eating a single mushroom weighing about 50 grams (containing 5 mg of toxin) is potentially lethal.[2] Whereas most of the reported cases of *A phalloides* poisoning have occurred in Europe, cases have increasingly been reported in the United States, especially on the West Coast.[1] *Amanita* mushrooms flourish from late summer to fall in temperate zones, have a proclivity for oak trees, and may grow on urban lawns. *Amanita phalloides* are large mushrooms, look appetizing, have no offensive taste to warn of their danger, and can be mistaken as an edible species, especially by amateur mycologists.[1,12–14] Because of the unusually warm weather in northern California during fall and winter in 1995 and 1996, fruiting *A phalloides* mushrooms were observed well past their normal season.

Amatoxins are heat-stable, cyclic octapeptides that preferentially affect rapidly dividing cells of the liver and gastrointestinal tract. Kidney, pancreatic, testicular, and lymphocytic cells are also affected. Amatoxins interfere with DNA transcription by inhibiting the synthesis of messenger RNA. Protein synthesis is disrupted, resulting in cell necrosis and death. Studies in dogs have shown that urinary elimination of this toxin is rapid, with 90% of an administered dose being eliminated within five hours. Hepatic uptake occurs through the bile salt transport system. There is substantial biliary excretion with an enterohepatic recirculation of toxin.[1,15]

The onset of symptoms is the most helpful clue as to whether *A phalloides* poisoning has occurred. Poisoning should be presumed to be due to amatoxin if there is a latency period of 6 to 24 hours following ingestion (mean, 10 to 12 hours), in contrast to an earlier onset for other mushroom poisonings. The gastrointestinal phase follows the latent period and is characterized by crampy abdominal pain, nausea, vomiting, and profuse watery diarrhea. This phase generally lasts for 12 to 24 hours and can be complicated by severe dehydration and electrolyte disturbances. Another latent period ensues at this point in which the patient feels better, but clinical measures usually show evidence of hepatic injury. Finally, the hepatic phase begins 48 to 96 hours after ingestion and is heralded by rising aminotransferase levels, coagulopathy, and jaundice. Encephalopathy, renal failure, and death from liver failure may ensue within two weeks.[1,2,16]

Formerly, fatality rates of more than 50% were common following the ingestion of *A phalloides*. Improved treatment procedures, aggressive management, and the development of liver transplantation have reduced the overall death rate to about 20%. The amount of mushroom ingested is the main prognostic indicator. Thus prompt intervention—gastric lavage and emesis—may have an important effect on limiting the amount of toxin absorbed and reducing mortality.[15]

The general principles for the treatment of amatoxin poisoning call for prompt and aggressive measures to reduce amatoxin absorption. Because removing even the smallest amount of amatoxin may improve the prognosis, inducing vomiting and gastric lavage with activated charcoal are recommended to remove any unabsorbed toxin from the gastrointestinal tract and to interrupt the enterohepatic cycle.[1,2,13] Extensive fluid loss from vomiting and diarrhea require aggressive rehydration with intravenous fluids.[1,13] In addition, because most of the amatoxin is excreted in large quantities in the urine during the first days following ingestion, it is imperative to maintain an adequate diuresis (100 to 200 ml per hour).[17] The value of extracorporeal techniques such as hemoperfusion and dialysis is limited unless they are used sooner than 36 hours after ingestion.[1] This may be due to the rapid elimination of amatoxin from plasma, usually before 48 hours.[17] Finally, although there is no specific antidote for amatoxin, the intravenous administration of high doses of penicillin and silibinin (the active ingredient in milk thistle) is recommended, as it is thought that they competitively inhibit amatoxin uptake by hepatocytes.[1,2,15] It is essential to consult with a poison control center and liver

transplantation unit early in the management of a patient with serious mushroom poisoning because hepatic failure can progress rapidly and organ procurement may require several days.[1] In our study, monitoring and gastric lavage were the primary procedures reported. This suggests that observation and symptomatic treatment were typically all that was required in these cases, again emphasizing the relatively favorable prognosis in most cases of poisonous mushroom ingestion. In addition, no liver transplantations were done for mushroom poisoning during the 1990 through 1994 time period.

Conclusion

The hunting and eating of wild mushrooms are increasing in popularity throughout the United States. Although most mushroom species are safe to eat, expert knowledge is essential to avoid the small risk of death and disability from mushroom toxins. Undersupervised young children are particularly at risk of suffering adverse effects from the ingestion of poisonous mushrooms. Parents should be warned explicitly about allowing unsupervised children free rein of their backyards, where mushrooms may be growing. Ethnic communities should be encouraged to seek information and assistance from local health authorities and mycologic societies about wild mushroom picking. In addition, clinicians should be aware of the possibility that eating a wild mushroom may be fatal, especially if symptoms begin after a six-hour latent period. Furthermore, because several types of mushrooms may grow near each other or be consumed together, the presence of early symptoms should not rule out the possibility of more serious poisoning. Finally, if amatoxin poisoning is suspected, prompt and aggressive treatment should be instituted, with arrangements for early consultation to a liver transplantation unit. Our study showed that in California, "serious" mushroom poisoning has a generally favorable prognosis if the patient reaches a hospital. It is up to public health officials, mycologic societies, and enthusiasts to provide education and expert knowledge to reduce the number of "accidental" ingestions of toxic mushrooms.

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Articles

Evaluation of Cerebrospinal Fluid in Southeast Asian Refugees With Reactive Serologic Tests for Syphilis

DEDRA BUCHWALD, MD; ANN C. COLLIER, MD; SHEILA A. LUKEHART, PhD; PHALLA KITH, PA-C; ERIKA GOLDSTEIN, MD; *and* THOMAS M. HOOTON, MD, *Seattle, Washington*

To determine the prevalence of cerebrospinal fluid abnormalities in Southeast Asian refugees with reactive serologic tests for syphilis, we evaluated 65 patients, 36 prospectively and 29 retrospectively, in a primary care clinic. Information was collected on history of treponemal infections, neurologic symptoms and signs, and total protein concentration, leukocyte count, and the VDRL test in the cerebrospinal fluid. Neurologic symptoms were reported by all patients for whom data were available. Abnormal neurologic signs were found or noted in medical records in 15 (42%) prospectively evaluated patients and 9 (64%) of 14 retrospectively evaluated patients for whom data were available. No patient had evidence of congenital or non-neurologic sequelae such as cutaneous or cardiovascular manifestations of syphilis. No patient had a positive cerebrospinal fluid VDRL test, 1 had more than 5 $\times 10^6$ leukocytes per liter (5 leukocytes per mm^3), and 6 (9%) had elevated total protein levels in the cerebrospinal fluid. Previous therapy for syphilis was not associated with lower serum VDRL reactions, neurologic symptoms and signs, or cerebrospinal fluid findings. In the absence of other indications, routine examination of the cerebrospinal fluid in seropositive Southeast Asian refugees who have nonspecific neurologic symptoms has a low yield, perhaps because of the high prevalence of yaws in this population, and may not be warranted.

(Buchwald D, Collier AC, Lukehart SA, Kith P, Goldstein E, Hooton TM: Evaluation of cerebrospinal fluid in Southeast Asian refugees with reactive serologic tests for syphilis. West J Med 1996; 165:289–293)

Syphilis remains a common disease worldwide despite readily available treatment. In the United States, an estimated 81,696 cases were reported in 1994.[1] The Centers for Disease Control and Prevention (CDC) recommends evaluating the cerebrospinal fluid (CSF) to screen for neurosyphilis in seropositive patients with symptoms or signs suggestive of neurosyphilis and in selected asymptomatic patients with reactive serologic tests for syphilis of more than a year's or an indeterminate duration.[2] The optimal diagnostic approach to Southeast Asian refugees with reactive serologic tests for syphilis is unclear because diagnosis is complicated by the high background prevalence of neurologic complaints; difficulty in obtaining an accurate medical history, including previous antibiotic treatment; and the frequent occurrence in Southeast Asia (30% to 50% prevalence in some Cambodian villages) of yaws, an endemic treponemal infection serologically indistinguishable from syphilis.[3]

In an attempt to determine the value of a neurosyphilis evaluation in Southeast Asian patients with reactive serologic tests for syphilis, we analyzed the clinical status and lumbar puncture results from 65 Southeast Asian patients who had reactive VDRL tests and confirmatory treponemal antibody tests on routine screening. In this article, we describe the clinical and laboratory findings in this group of patients.

Patients and Methods

Patients

For this study, we identified 65 patients (33 men and 32 women) from a log of seropositive Southeast Asian patients seen from 1979 to 1988 in the Refugee Health Clinic, a primary care clinic in which serum specimens for VDRL tests are routinely obtained at the initial visit, or in the Sexually Transmitted Diseases Clinic at Harborview Medical Center, Seattle, Washington. Each patient had a documented reactive VDRL and a positive treponemal antibody test (fluorescent treponemal antibody-absorption [FTA-ABS] test or microhemagglutination-*Treponema pallidum* test for syphilis) within 18

From the Department of Medicine, Harborview Medical Center, University of Washington School of Medicine, Seattle.
Reprint requests to Dedra Buchwald, MD, Harborview Medical Center, 325 Ninth Ave, Box 359780, Seattle, WA 98104.

ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control and Prevention
CSF = cerebrospinal fluid
FTA-ABS = fluorescent treponemal antibody-absorption [test]

months before CSF evaluation. All patients gave written informed consent before the lumbar puncture.

Of the 65 seropositive patients, 36 were examined prospectively (group A) and underwent, at the time of the CSF evaluation, a pupillary response and funduscopic and gait evaluation. A trained medical interpreter administered a standardized questionnaire to elicit information on neurologic symptoms and a history of signs, symptoms, and previous treatment of syphilis and yaws. Photographs were used to assist patients in identifying dermatologic manifestations of yaws. Medical records were reviewed for further evidence of neurologic symptoms or signs. After the lumbar puncture, consenting patients were treated with a regimen of 2.4 million units of benzathine penicillin given intramuscularly weekly for three weeks.

The cases of 29 seropositive patients who previously had undergone CSF evaluation because of a positive syphilis serologic test were evaluated retrospectively (group B). The patients' medical records were reviewed to abstract information on the variables that were assessed on the prospectively studied patients.

Data from neurologic examinations done before the lumbar puncture and on previous treatment of syphilis were abstracted from the medical records of all 65 patients using a standardized data form. These examinations were performed by a variety of physicians, including primary care physicians, neurologists, and other consultants. In all patients with neurologic signs, causes other than syphilis were sought by reviewing the patients' medical records. In addition to patients' local medical records, additional data on 48 of the study patients were obtained from the CDC to document previous treatment of possible syphilis before immigration.

Statistical Analyses

The Student's *t* test was used to examine differences in continuous variables. Comparisons between treatment groups were made using the χ^2 statistic and Fisher's exact test. For some of the analyses, we stratified patients into two groups depending on their syphilis treatment status. Patients were considered to have received previous treatment of syphilis if there was documentation in the medical record or from CDC records or if the patient provided an accurate description of a treatment regimen for syphilis.

Results

Patient Demographics and Clinical Characteristics

The 65 patients had the following ethnicity: 38 (58%) Cambodians, 15 (23%) Mien, 9 (14%) Vietnamese, and 3 (5%) Laotians. The mean age of the study patients was 46 years (range, 18 to 84 years), 32 (49%) were men, and for the 49 patients for whom data were available, the mean duration of residence in the United States before their lumbar puncture was 37 months (range, 3 to 95 months).

Among the 36 group A subjects, 4 (11%) reported a history of a genital ulcer, 6 (17%) of syphilis (including all 4 with a history of genital ulcer), and 3 (8%) of yaws. Neither documentation nor clinical confirmation was available to substantiate these reports. Of 30 who were asked, 6 (20%) (including 2 who reported having had yaws) reported that yaws (identified from the photographs) had occurred in their village. Clinical evidence of congenital syphilis or of non-neurologic sequelae of syphilis, such as cutaneous or cardiovascular manifestations, was not noted in the medical record of any patient. We did not specifically examine patients for these clinical signs, however.

Neurologic Symptoms

Neurologic symptoms reported by the patients are listed in Table 1. Neurologic symptoms were reported by all 36 patients in group A. Of these, 28 (78%) reported one or more of the following: tinnitus, hearing loss, shooting pains, loss of consciousness, or seizures. All 17 patients in group B for whom such information was available in the medical records had one or more neurologic symptoms. There was no mention of neurologic symptoms in the records of the other 12 group B patients. Multiple neurologic symptoms were present in 34 (94%) of 36 group A patients and 15 (88%) of 17 group B patients. The mean duration of each neurologic symptom was longer than four years (range, 3 weeks to 46 years), and there were no substantial differences between men and women.

Neurologic Signs

Neurologic abnormalities noted in study patients are listed in Table 2. None of the 36 group A patients had pupillary or funduscopic findings suggestive of syphilis, but 3 (8%) had a gait abnormality compatible with neurosyphilis at the time of the lumbar puncture. In addition, the mention of one or more neurologic findings was noted in the medical records at least once before the lumbar puncture in 15 (42%) of 36 group A patients, and 7 (19%) had two or more such abnormalities. Of 14 group B patients for whom a neurologic examination had been recorded in the medical record, 9 (64%) had a neurologic abnormality. Among these patients, three had a gait abnormality, one had a pupillary abnormality (due to previous cataract surgery), and one had dementia. Iritis, tabes dorsalis, or signs or symptoms compatible with these syndromes were not specifically mentioned in the medical records of any of the 50 patients for whom a neurologic examination had been recorded. Neurologic signs were considered to be attributable to conditions other than syphilis (such as spinal stenosis or polio) in 16 (67%) of the 24 patients with neurologic abnormalities.

TABLE 1.—*Neurologic Symptoms Reported by Study Patients*

Neurologic Symptom	*Group A** *No. With Symptom (%)*		*Group B†* *No. With Symptom/ No. With Presence or Absence of Symptom Noted in Chart (%)*	
Blurry vision or blindness	32	(89)	10/14	(71)
Dizzy spells	26	(72)	11/13	(85)
Headache	25	(69)	15/15	(100)
Tinnitus	20	(56)	7/10	(70)
Weakness	20	(56)	6/8	(75)
History of loss of consciousness‡	15	(42)	6/11	(55)
Hearing loss	12	(33)	5/12	(42)
Shooting pains in legs	11	(31)	0/10	(0)
History of seizures‡	1	(3)	4/10	(40)

*A standardized questionnaire was used to collect data on the 36 group A patients.
†Data were retrospectively abstracted from medical records of the 29 group B patients.
‡Self-reported, but documentation was generally not available.

Laboratory Findings

Serum VDRL titers were weakly reactive in 23 (36%), 1:1 in 23 (36%), 1:2 in 6 (9%), 1:4 in 6 (9%), 1:8 in 4 (6%), 1:16 in 1 (2%), and 1:32 in 1 (2%). Titers were 1:4 or greater in 12 (19%) of 64 patients (serum VDRL titer was not available on 1 patient). Data on CSF VDRL tests were not available for three patients, on CSF leukocyte counts for three patients, and on CSF protein for one patient. None of the 62 evaluable patients had a positive CSF VDRL test, and only one patient had a CSF leukocyte count of greater than 5×10^6 per liter (5 per mm^3). The CSF total protein level was higher than 0.45 grams per liter (45 mg per dl) in 6 (9%) of 64 patients. There were no associations between the serum VDRL titer or abnormal CSF values and age, sex, or duration in the United States, except that persons with a serum VDRL titer of 1:2 or greater had been in the United States for a shorter period of time before the lumbar puncture than those with a titer of less than 1:2 (mean of 18.7 months for 11 patients compared with 38.1 months for 37 patients, respectively).

Analysis of Untreated Patients

Of the 65 patients, 16 (25%) accurately described or had documentation of previous treatment of syphilis a mean of 26 months (range, 1 week to 86 months) before the lumbar puncture. The median serum VDRL titer in the 49 previously untreated patients was similar to that in the 16 previously treated patients. Evaluation of the 49 untreated patients revealed no associations between serum VDRL titer and CSF findings and the presence of neurologic symptoms and signs.

Discussion

The prevalence of reactive serologic tests for syphilis among Southeast Asian refugees ranges from 3 (1%) of 356 newly arrived refugees screened by a public health department[4] to 48 (12%) of 416 persons seen in a university-affiliated health center screening program.[5] In one study, Cambodians had a higher prevalence of seropositivity than other ethnic groups (19% versus 4%) ($P < .001$) and accounted for 83% of seropositive subjects.[5]

Evaluating seropositive Southeast Asian patients is a dilemma for two major reasons. First, it is impossible to distinguish, by serologic means, between syphilis and yaws, which is endemic in Southeast Asia. The prevalence of yaws is as high as 50% in children and 30% in adults in some Cambodian villages. Yaws is spread by nonvenereal means and causes early skin manifestations with subsequent effects on bone and cartilage. Although yaws infection will result in positive serologic tests for syphilis, it is not thought to involve the central nervous system. Because of its distinctive clinical appearance, recurrence pattern, and epidemiology, yaws generally can be distinguished from syphilis with reliable clinical and epidemiologic data. Such data, however, are often not available to clinicians caring for Southeast Asian refugees because of language barriers, difficulties in obtaining a reliable medical, sexual, and treatment history, and patients' lack of familiarity with medical terms. Despite the high prevalence of yaws in these groups, only a few of our patients reported a previous personal or village history of yaws.

Second, the high prevalence of neurologic symptoms and signs in Southeast Asian refugees complicates the decision as to whether CSF evaluation of seropositive patients is warranted. All 53 of our patients for whom data were available reported neurologic symptoms, and most reported multiple symptoms, usually in the absence of other identifiable causes. The high prevalence of neurologic symptoms may reflect depression, which is frequently manifested as somatization in this population. In this regard, Lin and co-workers found vague somatic symptoms in the absence of a clear cause in 34% to 75% of Southeast Asian refugees.[6] Others have found neurologic symptoms to be common: for example, in one study, 60% of Southeast Asian refugees complained of headaches.[7] In our study, 15 (42%) of 36 prospectively evaluated patients had a diagnosis of depression noted in their medical records. The frequent

TABLE 2.—*Neurologic Findings in Study Patients*

Neurologic Finding	Group A* No. With Finding/No. With Neurologic Exam in Chart	(%)	Group B† No. With Finding/No. With Neurologic Exam in Chart	(%)
Abnormal pupillary response	0/36	(0)	1/9	(11)
Abnormal funduscopic exam	0/36	(0)	0/12	(0)
Abnormal gait	3/36	(8)	3/12	(25)
Abnormal motor or sensory exam	9/33	(27)	4/13	(31)
Absent or asymmetric deep tendon reflexes	5/32	(16)	1/12	(8)
Abnormal cerebellar exam	2/22	(9)	4/10	(40)
Abnormal cranial nerve exam	2/31	(6)	2/13	(15)

exam = examination

*Pupillary response, funduscopic examination, and gait evaluation were done prospectively; data on other neurologic signs were abstracted from medical records in the 36 group A patients.
†All data were abstracted from medical records of the group B patients.

finding of somatization and depression accompanied by nonspecific neurologic symptoms underscores the need for guidelines on the appropriate diagnostic approach to Southeast Asian patients who have serologic tests reactive for syphilis.

The diagnosis of neurosyphilis in a seropositive patient is complicated by the lack of a diagnostic gold standard and the apparent lack of sensitivity and specificity of available tests. In general, an unexplained CSF leukocyte count of greater than 5×10^6 per liter or a CSF total protein concentration of greater than 0.45 grams per liter is compatible with neurosyphilis, but neither assay is specific.[8] Although a positive CSF VDRL test is considered diagnostic of neurosyphilis, its sensitivity is low, ranging from 22% to 69% in active neurosyphilis.[8] Other tests, such as the CSF FTA-ABS, that have been suggested for evaluating patients for neurosyphilis[9] were not used in this study because of uncertainties regarding their interpretation. In the absence of definitive clinical findings, a presumptive diagnosis of neurosyphilis may be made in seropositive patients with an unexplained CSF pleocytosis and elevated protein concentration or a reactive CSF VDRL test. Such was not the case in any of our 65 patients.

Before antibiotics were available, symptomatic late central nervous system involvement occurred in about 3.3% to 6.5% of patients with untreated syphilis.[10,11] Early studies also showed a high incidence of asymptomatic central nervous system involvement: 20% in early cases and 6.3% after 20 years.[12] Recent studies have confirmed the findings of these older studies, demonstrating evidence of asymptomatic central nervous system involvement in as many as 25% of untreated patients with late latent syphilis.[13] We would anticipate that the proportion with neurosyphilis among seropositive persons with neurologic symptoms or signs would be considerably higher. Thus, if our data on treatment history are accurate, we would have expected to find evidence of neurosyphilis in about 3 to 12 of the 49 patients for whom we had no documentation of previous therapy for syphilis. No clear evidence of neurosyphilis was found in any of 65 seropositive Southeast Asian patients, however, including those with presumed untreated disease, despite the high prevalence of neurologic symptoms and signs. Although the CSF protein concentration or leukocyte count was elevated in 7 (11%) of our patients, no patient had both pleocytosis and an elevated protein value, and the proportion with neurologic symptoms and signs was no different in patients with or without CSF abnormalities.

The evaluation of CSF is recommended in any patient who has positive serum VDRL and FTA-ABS tests and clinical signs or symptoms that suggest neurologic involvement.[2] Although a lumbar puncture is often done to rule out neurosyphilis in patients with syphilis of more than a year's or an unknown duration, criteria are provided for clinicians who want to tailor the decision to each patient.[2] Although we cannot conclude from our data that Southeast Asian refugees are at lower risk for acquiring neurosyphilis than are other populations, our study suggests that the yield of CSF examination in seropositive Southeast Asian refugees is lower than expected compared with other populations with syphilis. In our study group, it is possible that seropositivity resulted from yaws (often unrecognized clinically) rather than syphilis.

The ubiquitous nature of neurologic complaints among Southeast Asians makes the diagnosis of neurosyphilis based on clinical findings difficult. Although our data demonstrate a low yield of doing lumbar punctures on seropositive patients, there are several situations that warrant strong consideration for examination of the CSF. First, any patient with clinical evidence strongly suggestive of neurosyphilis—for example, objective evidence of pupillary or hearing abnormalities, bilateral loss of reflexes in the lower extremities, cognitive changes, or loss of vibration or position sense—should certainly have a CSF examination. Second, any patient who has a history of any sexually transmitted infection (including the human immunodeficiency virus) or who, because of sexual behavior, is at high risk for acquiring a sexually transmitted disease, should have a CSF examination. Last, lumbar puncture should be considered for patients with a high serum VDRL or rapid plasma reagin

titer (≥1:8), younger patients (≤40 years), and patients who may have recently acquired treponemal infection (in whom yaws would be less likely).

Because the low yield of CSF examination found in our patients may indicate yaws or previous treatment in this population, it should be emphasized that these findings cannot be extrapolated to the general population. In patients whose seropositivity is of more than a year or of unknown duration and who do not undergo lumbar puncture or who have no CSF abnormalities, we recommend therapy with a regimen of 2.4 million units of benzathine penicillin administered intramuscularly weekly for three consecutive weeks. This regimen is sufficient for the treatment of both uncomplicated syphilis and yaws. Patients with objective evidence of neurosyphilis should be treated with a recommended regimen for neurosyphilis.[2]

Our study has several limitations that possibly affect the ability to generalize our conclusions to other groups of Southeast Asian refugees. First, our sample size was small. Second, in our experience, in the absence of a strong, ongoing relationship with a health care professional, Southeast Asian patients are unlikely, because of cultural factors, to discuss sexual practices. In this study, most patients either did not have a single primary health care provider or the lumbar puncture was done by another physician. Last, because of the wide availability of, and frequent self-medication with, over-the-counter antibiotics in Southeast Asia, it is possible that many of our untreated patients had received therapeutic doses of antibiotics with antitreponemal activity. Nevertheless, this study suggests that routine CSF examinations are not warranted in seropositive Southeast Asian patients who have nonspecific neurologic symptoms in the absence of other indications. Treatment as described earlier with benzathine penicillin and appropriate follow-up should be adequate for such patients. On the other hand, we continue to strongly recommend that seropositive Southeast Asian patients who meet any of the criteria listed earlier should have an evaluation of their CSF to rule out the possibility of neurosyphilis.

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Conferences and Reviews

Hospital Volume Influences Outcome in Patients Undergoing Pancreatic Resection for Cancer

ROBERT E. GLASGOW, MD *and* SEAN J. MULVIHILL, MD, *San Francisco, California*

Surgical resection is the only possibly curative treatment of malignant pancreatic neoplasms, but major pancreatic resection for cancer is associated with high rates of morbidity and mortality. The objective of this study was to determine the relation between hospital volume and outcome in patients undergoing pancreatic resection for malignancy in California. Data were obtained from reports submitted to the Office of Statewide Health Planning and Development by all California hospitals from 1990 through 1994. Patient abstracts were analyzed for each of 1,705 patients who underwent major pancreatic resection for malignancy. Of the 298 reporting hospitals, 88% treated fewer than 2 patients per year; these low-volume centers treated the majority of patients. High-volume providers had significantly decreased operative mortality, complication-associated mortality, patient resource use, and total charges and were more likely than low-volume centers to discharge patients to home. These differences were not accounted for by patient mix. This study supports the concept of regionalizing high-risk procedures in general surgery, such as major pancreatic resection for cancer.

(Glasgow RE, Mulvihill SJ: Hospital volume influences outcome in patients undergoing pancreatic resection for cancer. West J Med 1996; 165:294–300)

In the United States, about 28,000 new cases of adenocarcinoma of the pancreas are diagnosed annually, accounting for about 2% of all cases of noncutaneous malignant neoplasms.[1] The only possibly curative treatment of pancreatic cancer is surgical resection. Enthusiasm for major pancreatic resection for malignancy has been dampened by reported operative mortality rates of 20% or greater and major morbidity rates of 40% to 60%.[2,3] Recently several large centers have reported operative mortality rates of less than 5% and major morbidity rates of about 30%.[4–9] It is not clear whether these improvements in operative outcome have occurred only in specialized centers or more generally in the medical community.

It is estimated that only 2,000 to 3,000 major pancreatic resections for malignancy are undertaken in the United States each year. The American College of Surgeons reports that 17,000 to 23,000 general surgeons are in active practice today in the United States.[10] An average general surgeon in the United States might do an operation of this sort once every 6 to 12 years. Similarly, the American Hospital Association reports that 6,539 acute care hospitals cared for patients in the United States in 1992.[11] If surgical therapy for pancreatic cancer were evenly distributed, such operations would be done only once every two to three years at a given hospital.

The relationship between experience with a medical therapy and outcome has been previously studied.[12–18] Luft and colleagues, for example, reported substantial improvements in hospital mortality in high-volume centers performing complex operations such as coronary artery bypass, whereas no such relationship was observed for less complex operations such as cholecystectomy.[12] Recent reports describing statewide data from Maryland and New York support a volume-outcome relationship for pancreatectomy.[19,20] This finding has been disputed in other population studies, such as the experience nationwide in the US Department of Veterans Affairs system, where no volume-outcome relationship was observed.[21]

A key goal of any reorganization of health care delivery practices in the United States is not only to reduce cost, but to preserve or improve quality. Quality of a surgical procedure is measured by operative morbidity and mortality, outcome, and effectiveness compared with alternative therapies. It is an open question today whether or not regionalizing high-risk procedures in general surgical practice is desirable or warranted from this standpoint. The goal of this study was to evaluate the relation between hospital volume and postoperative outcome in patients undergoing major pancreatic resection for malignancy in California. We hypothesized that the risk of this procedure, as measured by operative mortality, is reduced when performed in hospitals with greater experience.

From the Department of Surgery, University of California, San Francisco (UCSF), Medical Center.
Reprint requests to Sean J. Mulvihill, MD, UCSF Medical Center, 533 Parnassus Ave, U-122, San Francisco, CA 94143-0788.

ABBREVIATIONS USED IN TEXT

DRGs = diagnosis-related groups
ICD-9 = *International Classification of Diseases, 9th Revision, Clinical Modification*
OSHPD = Office of Statewide Health Planning and Development

Patients and Methods

The study design was a retrospective review of standardized patient discharge abstracts obtained from the California Office of Statewide Health Planning and Development (OSHPD). The reliability of this method in comparing differences in patient outcome was previously confirmed.[22-24] This database contains discharge data abstracts for every patient hospitalization from each acute care facility in California. Each abstract includes the following data: hospital identification, age group, sex, race, admission year, admission type (emergency, urgent, or elective), primary payer source, patient diagnosis (principal diagnosis and as many as 16 secondary diagnoses), procedure (principal procedure and as many as 16 secondary procedures), length of hospital stay, patient disposition, total hospital charges, and a measure of overall hospital resource use. Operative death in this study was defined as patient death before hospital discharge. The OSHPD database used diagnostic and procedural codes derived from the *International Classification of Diseases, Ninth Revision, Clinical Modification*, fourth edition (ICD-9), issued by the US Department of Health and Human Services.[25] Hospital resource use was measured by the determination of an Overall Resource Demand Scale (MedStat Group, Santa Barbara, California). This measure predicts the overall hospital resource use for a patient relative to a norm across all patients and diagnosis-related groups (DRGs). In this scale, the average acute care admission is assigned a value of 100. An overall resource demand value of 190, for example, indicates that the patient is predicted to require 90% more resources than the average of all patients across all DRGs.

All discharge abstracts from the years 1990 through 1994 were included in the initial search of the OSHPD database. From these abstracts, the cases of all patients who underwent total pancreatectomy (ICD-9 52.6), radical pancreaticoduodenectomy (ICD-9 52.7), proximal pancreatectomy (ICD-9 52.51), radical subtotal pancreatectomy (ICD-9 52.53), pancreatectomy unspecified (ICD-9 52.59), and distal pancreatectomy (ICD-9 52.52) were examined. From this group, a subset of patients undergoing pancreatic resection for malignancy was selected. These included patients with a primary diagnosis of cancer of the exocrine pancreas or islet cells (ICD-9 157.X), duodenum (ICD-9 152.0), bile duct (ICD-9 156.1), and the ampulla of Vater (ICD-9 156.2). This yielded a study population of 1,910 patients from 298 acute care facilities.

The role of individual patient characteristics in predicting operative mortality was assessed using univariate analysis, with statistical significance determined by the χ^2 test. Individual patient characteristics thought to be possible predictors of operative mortality included principal diagnosis, type of resection, year of surgery, age, sex, race, admission type, payer source, and the number of secondary diagnoses. The number of secondary diagnoses served as a measure of the severity of illness and as a means of comparing patient populations among hospitals.[20,26] In the OSHPD database, secondary diagnoses included comorbid medical problems not related to the malignant neoplasm (such as diabetes mellitus, hypertension, or chronic obstructive pulmonary disease), comorbid illnesses associated with the cancer (cholecystitis, cholangitis, pancreatitis, or obstruction), descriptors of disease stage (local invasion, lymph node status, and regional and distant metastases), and operative complications (hemorrhage, infection, or medical complications). Thus, both preoperative and postoperative conditions are listed in this database as secondary diagnoses.

A logistic-regression analysis was done to determine the relation between hospital volume and operative mortality while controlling for differences in individual patient characteristics. The patient characteristics identified earlier were treated as covariates. Operative death was the dependent variable. The role of each of the independent variables, including each of the individual patient characteristics and hospital volume, in predicting operative mortality was analyzed using this logistic-regression model.

Hospitals were classified into six arbitrary groups based on the number of pancreatic resections performed in the five-year study period. This classification ensured that the number of patients in each volume range was sufficiently large for statistical analysis. A crude mortality rate, discharge disposition profile (home versus other–death, skilled nursing facility, short-term care facility, and other), length of hospital stay, total hospital charges, and predicted resource use were calculated for each volume range. In addition, the frequency and outcome of the major operative complications, hemorrhage and infection, were determined. Differences among these measures of outcome were analyzed by analysis of variance. χ^2 Analysis of contingency tables, linear-regression analysis, and Wilcoxon or Kruskal-Wallis rank-sum test were used where appropriate. A P value of less than .05 was considered statistically significant.

An indirectly standardized mortality rate was calculated as described previously.[15,20,27] Briefly, a multiple-regression analysis was done using the patient characteristics found to be predictive of operative death by the corresponding logistic-regression model, yielding a predicted probability of death for each patient. This probability was then used to calculate an indirectly standardized or risk-adjusted mortality for hospitals, controlling for differences in patient characteristics at the time of admission among the different hospitals.

TABLE 1.—*Types of Pancreatic Resections and Associated Operative Mortality*

Pracedure	*Potients, Na.*	*Operative Martality, %*
Pancreaticoduodenectomy	1,424	9.4
Proximal subtotal pancreatectomy	158	8.9
Total pancreatectomy	123	16.3*
Distal pancreatectomy	205	1.0*

*$P < .05$ by χ^2 test compared with pancreaticoduodenectomy.

TABLE 2.—*Year of Surgery and Associated Operative Mortality*

Year	*Hospitals, No.*	*Patients, Na.*	*Deaths, No. (%)*
1990	157	316	38 (12.0)
1991	147	313	33 (10.5)
1992	168	346	23 (6.6)
1993	155	354	36 (10.2)
1994	162	376	38 (10.1)
Total	298	1,705	168 (9.9)

TABLE 3.—*Primary Tumor Location and Associated Operative Mortality*

Diagnasis	*Patients, Na.*	*Operative Mortolity, %*
Pancreatic cancer	1,051	10.2
Ampulla of Vater cancer	350	8.3
Bile duct cancer	151	10.6
Duodenal cancer	140	11.4
Islet cell cancer	13	0

*Not significant by χ^2 analysis.

Results

From 1990 through 1994, a total of 1,910 patients underwent major pancreatic resection in California for peripancreatic cancer. Most of the operations (Table 1) were pancreaticoduodenectomies or Whipple procedures (83.5% of patients). These patients were treated with an overall operative mortality of 9.4%. A smaller number of patients underwent proximal subtotal pancreatectomy (9.3% of patients) or total pancreatectomy (7.2% of patients). The mortality for total pancreatectomy was significantly higher than that for Whipple resection (Table 1). Distal pancreatectomy was done in 205 patients, with an operative mortality of 1.0% (2 of 205 patients). Because of this low operative mortality and the relatively small number of patients, a volume-outcome relation for distal pancreatectomy could not be determined. These patients were excluded, leaving 1,705 patients for further analysis.

The number of resections performed each year increased slightly from 316 in 1990 to 376 in 1994 ($P = .01$ by linear-regression analysis) (Table 2). A total of 298 hospitals reported to the database, but because not all hospitals treated patients undergoing pancreatic resection each year, the average number of reporting hospitals on a yearly basis was 158 (Table 2). The operative mortality for major pancreatic resection was similar from year to year, with an overall average of 9.9% (Table 2). The most common principal diagnosis was pancreatic cancer, accounting for 62% of patients (Table 3). This was followed by carcinoma of the ampulla of Vater (21% of patients), carcinoma of the distal bile duct (9% of patients), duodenal cancer (8% of patients), and islet cell cancer (0.8% of patients). No significant differences were found in operative mortality when stratified by principal diagnosis (Table 3).

Patient Demographics

Patient demographic information analyzed included age, sex, race, admission type, the number of secondary diagnoses, and source of payment. The age range of the study population was 2 to 85 years, with a median age of 65 years. Of the 1,705 patients, 70% were 60 years of age or older (Table 4). The operative mortality was directly related to advancing age ($P < .0001$ by χ^2 test). The number of men and women was similar, but men had a significantly higher operative mortality ($P = .006$ by χ^2 test). The most common race of treated patients was white (75% of the study group), followed by Hispanic (12%), Asian (7%), and black (6%). Operative mortality did not differ significantly according to race (Table 4). In contrast, the source of payment for care was associated with significant differences in operative mortality. Patients whose hospital stays were paid for by government programs (Medicare or Medi-Cal [California's Medicaid]) had higher operative mortality than did patients enrolled with private insurers, including Blue Cross or Blue Shield, health maintenance organizations, preferred health plans, and private insurance companies ($P < .0001$ by χ^2 test). These data are summarized in Table 4.

Admission type and number of secondary diagnoses were analyzed as indicators of the severity of illness. Patients admitted electively for resection had lower operative mortality than unscheduled patients admitted on an emergent or urgent basis (8.1% versus 12.5%, $P < .0001$) (Table 4). Common preoperative comorbidities included diabetes mellitus (ICD-9 250) in 18% of patients, essential hypertension (ICD-9 401) in 18%, coronary artery disease (ICD-9 412 through 414) in 14%, congestive heart failure (ICD-9 428) in 4%, chronic obstructive pulmonary disease (ICD-9 490 through 496) in 7%, nutritional deficiencies (ICD-9 260 through 263) in 5%, and chronic liver disease (ICD-9 571) in 2% (Table 5). An increased number of secondary diagnoses correlated with increased operative mortality (Table 4). For patients with fewer than four secondary diagnoses, operative mortality was 3.7%. This rate increased significantly with an increasing number of secondary diagnoses ($P < .0001$). The overall incidence of postoperative hemorrhage was 10.1%, with a 25% associated mortality. The overall incidence of postoperative intra-abdominal infection was 14.5%, with an 18% associated mortality. Both complications were predictive of operative death ($P < .001$).

Univariate analysis of individual patient characteris-

tics showed that age, sex, admission type, operation performed, number of secondary diagnoses, and payer source were significant predictors of higher operative mortality. The year of operation and race were not significant factors. These characteristics were analyzed further in a logistic-regression model. When hospital volume was excluded from the logistic-regression analysis, advancing age, male sex, the need for total pancreatectomy, and increasing number of secondary diagnoses were found to be statistically significant predictors of operative mortality (Table 6). When hospital volume was included in the model, these independent variables remained significant. Likewise, decreasing hospital volume was found to be significant ($P < .001$).

Hospital Volume-Outcome Relationship

Hospitals were grouped into six volume ranges reflecting the number of resections performed at each hospital from 1990 through 1994. More than half of all patients were treated at centers where ten or fewer resections were performed in the five-year study period (Table 7). These centers with low volume of pancreatic surgery accounted for 88% of all reporting hospitals. The highest volume centers treated more than 50 patients each during the study period, but these accounted for only 1% of the reporting hospitals and 8% of the treated patients.

Several measures of outcome were evaluated, including length of hospital stay, total hospital charges, overall resource use, and operative mortality. The length of hospital stay did not vary significantly among the different volume groups (Table 8). Total hospital charges decreased from the lowest volume group to the highest volume group—$87,857 versus $71,588. These differences among groups were significant by linear-regression analysis and the rank-sum test ($P < .0001$). The mean resource-demand scale score for all treated patients was 769. This means that the average patient undergoing pancreatectomy required 669% more resources than the average hospital admission across all DRGs (resource scale score of 100). Overall resource use decreased significantly as hospital volume increased ($P < .0001$ by linear-regression analysis and rank-sum test). In addition, high-volume centers were more likely to discharge patients to home than lower-volume centers (95% of patients versus 74% of patients, $P < .0001$ by linear-regression analysis and P test). The remaining patients either died or were discharged to an intermediate-care facility.

The outcome data for patients treated at centers with 31 to 50 cases were influenced by outliers. One center in this group had an average total hospital charge of $208,739. If this hospital was excluded from the group, the average charge for the remaining three centers was $75,241 (range, $57,933 to $96,804). The relationship between hospital volume and charges was strongly significant even when this outlier was included in the analysis. Likewise, an additional center in this group had an average length of hospital stay of 34.8 days. If excluded, the average length of hospital stay for this group falls from 23.9 to 20.2 days (range, 17.6 to 23.4).

TABLE 4.—*Patient Characteristics and Associated Operative Mortality*

Patient Characteristic	Patients, No.	Operative Mortality, %	P Value*
Age, yr			< .0001
<45	120	2.5	
45-59	408	4.9	
60-74	893	11.8	
≥75	284	14.1	
Sex			.006
Male	862	11.8	
Female	843	7.8	
Race			.22
White	1,272	9.4	
Black	97	8.3	
Hispanic	192	11.9	
Asian	114	13.2	
Other	30	10.0	
Admission type			.01
Emergent	98	13.3	
Urgent	601	12.3	
Elective	1,006	8.1	
Secondary diagnosis, No.			< .0001
0 to 4	641	3.7	
5 to 8	606	6.8	
9 to 12	294	19.0	
>12	164	28.7	
Payer source (all)			.002
Medicare	799	12.9	
Medi-Cal†	147	9.5	
Blue Cross or Blue Shield	75	5.3	
Insurance Company	238	5.9	
HMO or PHP	371	7.5	
Other	75	6.7	
Payer source (government versus private)			< .0001
Government payer	986	12.3	
Private insurer	719	6.5	

HMO = health maintenance organization, PHP = preferred health plan

*By χ^2 testing.
†California's Medicaid program.

There were small differences in the distribution of some of the preoperative comorbid medical diagnoses among the six hospital volume groups. For cholecystitis, cholangitis and biliary obstruction, pancreatitis, congestive heart failure, and chronic liver disease, these differences achieved statistical significance. This is summarized in Table 5. No significant differences were seen in the overall number of comorbid medical diagnoses among the six hospital volume groups. Further, no significant differences were seen when comparing predicted mortality rates for each volume group. The overall predicted mortality was 9.9% and ranged from 8.1% in the 21- to 30-volume group to 10.6% in the 6- to 10-volume group.

The overall mortality for the study population was

TABLE 5.—*Distribution of Comorbidities in Hospital Volume Groups*

Comorbidity	*1 to 5 Cases, %*	*6 to 10 Cases, %*	*11 to 20 Cases, %*	*21 to 30 Cases, %*	*31 to 50 Cases, %*	*>50 Cases, %*	*Overall*	*P Value*
Chronic obstructive pulmonary disease	6.7	8.9	6.6	5.7	4.7	3.5	6.6	NS
Coronary artery disease	15	18	20	19	20	23	14	NS
Congestive heart failure	5.7	4.6	3.5	4.0	0.5	1.4	3.9	< .05
Hypertension	15	18	20	19	20	23	18	NS
Diabetes mellitus	20	18	19	21	16	11	18	NS
Chronic renal failure	0.2	0	0	0	0	0	0.1	NS
Chronic liver disease	3.3	1.5	0	1.3	3.5	2.8	2.1	< .05
Mesenteric or peripheral vascular disease	0.4	1.0	0.8	0.9	2.3	1.4	0.9	NS
Malnutrition	5.7	6.1	6.2	3.1	5.9	2.1	5.2	NS
Average No. of comorbidities/patient	1.6	1.6	1.6	1.5	1.5	1.5	1.6	NS

NS = not significant

*By χ^2 testing.

TABLE 6.—*Logistic Regression Analysis**

Independent Variable	*P Value*
Year of operation	NS
Increasing age	< .05
Male sex	< .05
Race	NS
Admission type	NS
Payer source	NS
Total pancreatectomy versus other resections	< .005
Increasing number of secondary diagnoses	<.0001
Decreasing hospital volume	< .001

NS = not significant

*Dependent variable is operative mortality.

TABLE 7.—*Hospital Volume Assignments*

Hospital Volume	*Hospitals, No. (%)*		*Patients, No. (%)*	
1 to 5	210	(70)	510	(30)
6 to 10	53	(18)	395	(23)
11 to 20	20	(7)	258	(15)
21 to 30	9	(3)	228	(13)
31 to 50	4	(1)	171	(10)
>50	2	(1)	143	(8)

9.9%. Crude operative mortality decreased with increasing hospital experience, from 14.1% in low-volume centers to 3.5% in high-volume centers (Table 8). This relationship was significant (P = .0009 by linear-regression analysis and χ^2 test). The crude mortality for each volume group was risk-adjusted to account for significant differences in patient characteristics at admission as determined by logistic-regression analysis (Table 6). With this adjustment, a significant volume-outcome relationship persisted (Table 8).

The incidence of the two major postoperative complications, intra-abdominal hemorrhage and infection, did not differ significantly among the volume groups. The mortality associated with these complications, however, decreased as hospital volume increased. The operative mortality associated with hemorrhage and infection was 40% and 27%, respectively, in patients treated at low-volume centers compared with 11% and 11% at high-volume centers. These relationships were significant by linear-regression analysis (P = .02 for hemorrhage and .007 for infection).

Discussion

In this period of limited resources, increased attention is being paid in the United States to the most efficient provision of health care services. The desired goal is to provide the highest quality of care while using the fewest resources. It has been suggested that for certain complex surgical procedures, including heart transplantation, coronary artery bypass, and hip replacement, the results of treatment are directly linked to experience, as measured by yearly hospital volume.[13-16] We examined the possible relation between hospital volume and outcome in patients undergoing major pancreatic resection for malignancy.

The main finding in this study was a significant relationship between hospital volume and operative mortality for patients undergoing pancreatic resection for malignancy in California from 1990 through 1994. The sample size was large, encompassing 1,705 patients treated at 298 hospitals. The effect of hospital volume on operative mortality was large, with a fourfold difference in results between the lowest and highest volume providers. There are three possible explanations for this finding. First, it is possible that the data are flawed and that systematic reporting or coding errors favor the highest volume providers. In previous studies of population database reliability, a 10% to 30% error rate in diagnosis and procedure coding has been reported.[22,24,28] In this study, concordance between diagnosis and procedure codes was

TABLE 8.—*Hospital Volume Outcome Measures*

Hospital Volume, No.	*Length of Hospital Stay, days**	*Total Charges, $†*	*Overall Resource Scale†*	*Patients Discharged to Home, %‡*	*Crude Mortality, %‡*	*Risk-Adjusted Mortality Rate, %‡*
1 to 5	22.7	87,857	832	74.3	14.1	14.1
6 to 10	22.7	76,593	813	80.0	10.4	9.6
11 to 20	22.9	78,003	804	81.8	8.9	8.7
21 to 30	20.2	70,959	626	92.1	5.7	6.9
31 to 50	23.9	111,497	711	87.1	8.2	8.3
>50	20.5	71,585	652	95.1	3.5	3.5
Mean	22.3	83,479	769	82.1	9.9	9.9

*Not significant by rank-sum test. †$P < .0001$ by linear regression and rank-sum test. ‡$P < .0001$ by linear regression and χ^2 test.

required for each patient as part of the inclusion criteria, thereby reducing the number of erroneously coded patient discharge abstracts from further analysis. An error rate of only 1% has been identified in the reporting of the end point of patient death when the OSHPD database has been reconciled with primary data from individual patient medical records.[22] This error rate is not sufficiently large to explain the differences in operative mortality found between low- and high-volume hospitals in this study.

Second, it is possible that differences in patient characteristics could account for the observed variations in operative mortality. A number of patient characteristics were found to be significantly associated with the risk of postoperative death by logistic-regression analysis in this study, including age, male sex, the need for total pancreatectomy, and increasing number of secondary diagnoses. We controlled for patient characteristic differences in two ways. First, the data were pooled by hospital volume so that the number of patients in each volume group was sufficiently large to offset small differences in patient mix at any one hospital. Second, we adjusted crude operative mortality rates with the patient characteristics found to be significant in the logistic-regression model to arrive at a risk-adjusted mortality within each volume group. This risk adjustment did not alter the primary finding of a significant association between hospital volume and operative mortality. It is possible that risk factors for higher operative mortality were present but not identifiable in the OSHPD database and that the distribution of patients with this unknown risk factor was skewed toward hospitals with low volume, but this seems unlikely.

Finally, it is probable that the findings in this study represent true differences in outcome related to differences in patient care in hospitals of various volume groups.

A number of pieces of supporting evidence suggest that this last interpretation of the data is correct. First, the overall operative mortality of 9.9% in this study is comparable with previously reported operative mortality rates in other large population studies, including the nationwide Department of Veterans Affairs experience and a nationwide survey by the American College of Surgeons.[21,29] Second, the operative mortality of the highest volume centers in this study mirrors the published results of other high-volume centers around the world.[4,6–9] Finally, two recent studies have examined the relationship between hospital volume and operative mortality for pancreatic resection in the states of Maryland and New York.[19,20] The findings in these two reports and the current study are in remarkable agreement.

Only a limited insight into possible differences in patient care leading to improved operative mortality in the high-volume centers could be gleaned from the OSHPD database. Whereas the rates of major operative complications of hemorrhage and infection were similar in all hospital volume groups, the mortality associated with these complications decreased significantly with increasing hospital volume. This suggests that high-volume centers have developed either effective treatment strategies or the necessary supporting team to cope with these problems or both. The number of deaths associated with hemorrhage or infection was relatively small and did not account for the entire observed differences in operative mortality. Thus, other factors must be important, although these could not be identified with the available data.

In addition to reduced operative mortality, high-volume centers were found in this study to have reduced hospital charges and resource-demand scale scores. These were independent of length of hospital stay, which did not vary significantly among volume groups. High-volume centers were significantly more likely to discharge patients home, whereas low-volume centers used significantly more intermediate-care facility resources. Although an examination of actual costs would be preferable to these indirect measures of resource use, cost data were not available in this database. The above findings suggest, however, that the highest volume hospitals not only treat patients undergoing pancreatic resection for malignancy with substantially lower operative mortality, but also accomplish this with lower costs. If the standard of care defined by the highest volume hospitals were applied statewide in 1990 through 1994, 108 additional patients would have survived their operation, with a savings of $20,580,099 in hospital charges.

In today's health care environment, quality of care is measured not only in patients' clinical outcome, but also in cost-effectiveness. In California, most patients undergoing pancreatectomy for malignancy were treated at

hospitals with limited experience. This study shows a strong relationship between hospital volume and outcome in these patients. The data support regionalizing high-risk general surgical procedures, like pancreatectomy for malignancy, as a means of providing the most efficacious and cost-effective care.

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Epitomes

Important Advances in Clinical Medicine

Nuclear Medicine

David K. Shelton Jr, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in nuclear medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Nuclear Medicine of the California Medical Association, and the summaries were prepared under the direction of David K. Shelton Jr, MD, and the panel.

Radiation Synovectomy

RADIONUCLIDE THERAPY in joint diseases offers physicians a cost-effective alternative method for treating inflammatory arthritis when standard methods of treatment such as oral anti-inflammatory drugs, intra-articular steroids, sclerosing agents, or surgical synovectomy fail. The most common indications for synovectomy are rheumatoid arthritis, psoriatic arthritis, calcium pyrophosphate disease, hemophiliac arthropathy, and pigmented villonodular synovitis. Much of the experience with radiation synovectomy comes from Europe, although its use in the United States is growing slowly.

Desirable radionuclides are those with beta-particle emissions capable of treating or destroying inflamed and diseased synovium. Beta particles are effective and have limited collateral effects because radiation from the beta particles travels only about 1 to 3 mm in soft tissues. Many radiocolloids have been used experimentally for synovectomy, including yttrium Y 90, chromic phosphate P 32, dysprosium Dy 165, holmium Ho 166, and rhenium Re 186. ^{32}P-Chromic phosphate is the only radiopharmaceutical agent in the United States approved by the Food and Drug Administration for radiation synovectomy, although ^{90}Y has been used extensively in Europe.

All major and minor joints including the interphalangeal joints can be treated with synovectomy, although the knee is most commonly treated. The technique is straightforward and safe. The knee is fully extended, prepared with povidone-iodine solution, and then the site of administration is anesthetized with a solution of 1% lidocaine. An 18-gauge needle is inserted medial to the patella, the joint space is entered, and fluid easily withdrawn. Technetium Tc 99m sulfur colloid (1 mCi, 37 MBq) is administered, and images are obtained to show the distribution of activity throughout the joint space. A common cause of treatment failure is the presence of adhesions or loculations preventing the spread of the tracer throughout the joint. ^{32}P-Chromic phosphate (6 mCi, 222 MBq) is administered to the knee joint, followed by the administration of 20 mg of triamcinolone as the needle is slowly removed. The knee is extended and flexed several times to distribute the agent throughout the joint space. The patient is placed in a knee immobilizer and instructed to restrict activity for 48 hours to lessen the risk of leakage into the soft tissues and lymphatic system.

Satisfactory results with resultant clinical improvement have been reported in 78% to 84% of patients having radiation synovectomy. This procedure with the use of ^{32}P-chromic phosphate is safe, has relatively low radiation exposure, and is efficacious in the management of patients with inflammatory arthritis not responsive to the usual treatment modalities. No serious side effects have been found as much as ten years after treatment.

ERNO J. GYETVAI, MD
CHARLES W. SUTTER, MD
Sacramento, California

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Radiodosimetry in Nuclear Medicine

MANY OF THE EXAMINATIONS in nuclear medicine compare favorably with other diagnostic examination modalities in radiology with regard to patient dose. Several examples of diagnostic examinations in nuclear medicine provide information similar to that obtained by conventional radiography or fluoroscopy at substantially lower doses.

Just as not all radiation is equally damaging after a given absorbed dose, not all tissues are equally radiosensitive to its effects. Laboratory and epidemiologic investigations have shown that some tissues (for example, bone marrow) are at greater risk of radiogenic cancer and other stochastic effects after a given equivalent dose than other tissues (such as bladder). Tissue-specific organ-weighting factors (w_T) have been established to assign a particular organ or tissue (T) the portion of the stochastic risks resulting from the irradiation of that tissue compared with uniform whole-body irradiation. Tissue-weighting factor values range from 0.01 (for example, for skin) to 0.2 (for gonads), and the sum of all w_T equals one. The sum of the products of the equivalent dose to the organ or tissue (H_T) and the tissue-weighting factor (w_T) for each organ or tissue irradiated is called the "effective dose" (H_E)—that is, H_E (Sv) = $\Sigma\, w_T \times H_T$ (Sv). The effective dose is expressed in the same units as the equivalent dose (sievert or rem).

The effective dose provides a means to compare the risk or possible detriment between various x-ray and nuclear medicine examinations. While the procedures compared here do not provide exactly the same diagnostic information, the advantages with regard to patient dose from some nuclear medicine examinations are evident. For example, a radionuclide gastroesophageal reflux examination using 300 μCi of technetium Tc 99m sulfur colloid results in an H_E of about 0.3 mSv (0.03 rem) compared with an upper gastrointestinal examination with an H_E of about 2.4 mSv (0.24 rem). Some nuclear medicine tests not only result in a lower patient dose, but also have a diagnostic advantage relative to their radiographic counterpart. For example, radionuclide cystography is more sensitive for vesicoureteral reflux than contrast cystography and (for young women) results in an ovarian dose more than 50 times lower. These advantages of the nuclear medicine examinations are obtained at approximately the same cost as their x-ray counterpart.

In addition to minimizing patient dose, some nuclear medicine examinations have the following advantages: providing whole-body surveys that would otherwise require multiple computed tomographic scans or plain film radiographs (for example, tumor imaging with gallium citrate Ga 67 and skeletal imaging with technetium Tc 99m medronate), providing functional as well as anatomic information (for example, renal imaging with technetium Tc 99m mertiatide), and providing organ or tissue perfusion information (for example, cardiac perfusion with technetium Tc 99m sestamibi).

When diagnostic x-ray examinations require extended periods of fluoroscopy and cine radiography, alternative nuclear medicine procedures can provide lower dose alternatives. Examples include pulmonary arteriograms versus radionuclide ventilation-perfusion imaging and coronary arteriograms or ventriculography versus radionuclide cardiac perfusion or wall-motion studies. In these examples, not only is there an advantage to the nuclear medicine examinations with respect to H_E, but they also avoid the morbidity and mortality (albeit infrequent) associated with these invasive procedures, and are substantially less expensive.

JERROLD T. BUSHBERG, PhD, DABMP
Sacramento, California

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Scintimammography—A New Tool for Breast Cancer Diagnosis

BREAST CANCER is the second most frequently diagnosed malignant neoplasm among North American women, and its incidence is increasing at a rate of 3% per year. The high morbidity and mortality warrant an aggressive approach to the diagnosis and treatment of carcinoma of the breast. Three methods are currently used for breast cancer screening: breast self-examination, breast examination by a physician, and mammography; together they have a sensitivity of 85%. Mammography has a positive predictive value of only 15% to 30%. Abnormalities identified by screening must be evaluated for malignancy by breast biopsy, with its associated physical, psychological, and economic sequelae. A number of techniques, including ultrasonography, computed tomography, magnetic resonance imaging, positron-emission tomography, and scintimammography (SMM), are currently being evaluated as non-invasive means of characterizing breast abnormalities.

The technique of prone dependent-breast SMM is being used to characterize mammographic or clinical findings. Patients receive technetium Tc 99m sestamibi (a cationic lipophilic radiopharmaceutical routinely used in myocardial perfusion imaging) intravenously, and lateral images are acquired with the patient in the prone position and with the breast dependent from the imaging table. In 153 lesions for which breast biopsy was warranted, the sensitivity of SMM was 92%, specificity was 89%, the positive predictive value was 81%, and most important, the negative predictive value for the detection of carcinoma of the breast was 96%. The uptake of ^{99m}Tc-sestamibi has been shown to be generally independent of dense breast tissue found on mammography. Preliminary results of a multicenter trial of 673 patients in the United States and Canada show that sensitivity was 85%, specificity was 81%, the positive predictive value was 74%, and the negative predictive value was 90%.

Scintimammography has high sensitivity and improves the specificity of conventional mammography for the detection of carcinoma of the breast. It is currently being evaluated as a technique to possibly reduce the number of biopsies of the breast that yield negative results for

carcinoma. It can be used to resolve difficult cases such as women with breast implants or very dense breasts and those who have had surgical or radiation therapy.

IRA J. KHALKHALI, MD, FACR
LINDA DIGGLES, CNMT
Torrance, California

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Cholescintigraphy in Acute and Chronic Gallbladder Dysfunction

GALLBLADDER DISEASE remains a common diagnostic dilemma. More than 20 million Americans have gallstones, and yet less than half of them will ultimately have symptoms of acute or chronic cholecystitis. Anatomic studies such as ultrasonography or computed tomography may detect the presence of gallstones but are not as sensitive to their functional relevance. Functional imaging of the gallbladder and hepatobiliary system with cholescintigraphy can help to make the specific diagnosis or can exclude gallbladder dysfunction. Most patients with acute or chronic cholecystitis have gallstones. About 5% of patients with acute cholecystitis, however, have acalculous cholecystitis due to functional obstruction of the cystic duct with secondary inflammation or infection of the gallbladder and gallbladder wall. It is also estimated that about 5% of patients with chronic cholecystitis have acalculous chronic cholecystitis. In addition, chronic intermittent symptoms of acalculous gallbladder dysfunction due to the cystic duct syndrome and gallbladder dyskinesia can develop.

Functional imaging of the liver, gallbladder, and hepatic ducts is accomplished after the intravenous administration of a technetium Tc 99m-iminodiacetic agent that is rapidly extracted by the liver and excreted into the common bile duct, gallbladder, and small bowel. Cholecystokinin (CCK) or morphine sulfate can be administered as part of the examination to increase the certainty or efficiency of the examination. Biliary sludge may develop in patients with prolonged fasting, and pretreatment with CCK (0.02 μg per kg of body weight) may further reduce the number of false-positive examinations. Low doses of morphine (0.04 mg per kg) can be used to enhance the tone at the sphincter of Oddi, thereby shortening the time for radiotracer to fill the gallbladder. Visualization of the gallbladder essentially excludes acute cholecystitis with a negative predictive value of 99%. Nonvisualization of the gallbladder at one hour and four hours is highly diagnostic of acute cholecystitis. Nonvisualization of the gallbladder at one hour with delayed visualization at four hours strongly suggests chronic cholecystitis. The sensitivity and specificity for cholescintigraphy in acute cholecystitis are both greater than 95%. The reported sensitivity for the ultrasonographic diagnosis of acute cholecystitis is 24% to 86%, and the specificity is 60% to 77%, depending on whether strict or liberal criteria are used.

An abnormal gallbladder ejection fraction after intravenous CCK stimulation can help to diagnose chronic acalculous cholecystitis and other acalculous disorders such as the cystic duct syndrome and gallbladder dyskinesia. A gallbladder ejection fraction of less than 35% implies dysfunction and indicates that symptomatic patients may benefit from cholecystectomy even if ultrasonography is normal. Biliary scintigraphy using CCK may also help to detect sphincter of Oddi dysfunction, which can mimic gallbladder disease. In these cases, sphincterotomy rather than cholecystectomy may be the treatment of choice.

DAVID K. SHELTON, MD
ROBERT C. STADALNIK, MD
Sacramento, California

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Role of Lung Scanning in Patients With Pulmonary Embolism

PULMONARY EMBOLISM is primarily a manifestation of venous thromboembolism. The major risk factors in a recent large prospective investigation of pulmonary embolism diagnosis (PIOPED) were immobilization for three days or longer, a major operation within the past three months, trauma to the lower extremities, and central venous manipulation. In PIOPED patients without one of these major risk factors, but with suggestive signs, symptoms, and clinical risk factors, the prevalence of embolism was about 20%; in those who, in addition, had one major risk factor, the prevalence was about 30%; in those with two or more major risk factors, the prevalence was 40%.

The utility of the lung scan depends on the results. A normal lung scan is the most useful because it excludes clinically important embolism. This occurs in about 20% to 30% of large series. A scan with two or more medium-sized areas that are aerated but not perfused—one in patients without cardiopulmonary disease—("ventilation-perfusion mismatch"), occurs 16 times as frequently in

patients with embolism as without. Likelihood ratios (true-positive divided by false-positive results) of more than 10 or less than 0.1 alter prior probabilities enough to influence diagnostic decisions.

A "high-likelihood" lung scan finding means an embolism is likely present. This occurs in about 15% to 20% of series, but only 40% of persons with pulmonary embolism have this result. Most patients with embolism (60%) have "intermediate-," "low-," or very-low-outcome" scans. A "very-low-outcome" result has a likelihood ratio of 0.06, indicating that the presence of an embolism is unlikely. An "intermediate-outcome" result has a likelihood ratio of 1.28, so the prior probability is insignificantly changed by the scan results. This result often occurs in patients with a focal infiltrate on the chest film. The problem with a "low-outcome" scan is that it has a likelihood ratio of 0.33. Thus, when a patient is at high risk for pulmonary embolism with a 40% prior probability, a low-outcome scan still leaves a post-test probability of 18% and does not exclude embolism. A Canadian working group thinks the "low-likelihood-outcome" reading should be abandoned, especially in patients with severe cardiopulmonary disease.

The introduction of spiral computed tomography provides a less invasive alternative to pulmonary angiography for documenting the presence of substantial pulmonary embolism. It may also distinguish between acute and chronic embolism. The advantage of direct demonstration of an embolus is that it leads to a therapeutic decision.

Currently, however, the best first-line approach may be the documentation of the presence or absence of venous disease in conjunction with a lung scan and chest film. Excluding venous disease by appropriate methods indicates there is nothing to treat, and, in fact, such patients who are untreated have a less than 0.1% probability of an embolic event. In this country, duplex ultrasonography with compression is most widely used, even though it is operator dependent and may be difficult to apply in obese patients and those with casts, extremity injuries, or a recent surgical procedure. Lung scanning and evaluating the deep veins in those with nondiagnostic ("intermediate-" or "low-likelihood") lung scan results can settle the question of pulmonary embolism noninvasively in about 70% of cases.

Finally, because the vast majority of patients who undergo lung scanning do not have pulmonary embolism, a radionuclide study can frequently shed light on the pathophysiology of the clinical problem; for example, poorly aerated areas that are relatively well perfused usually result from acute airway obstruction.

FRED MISHKIN, MD
Torrance, California

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Use of Bone Mineral Measurements in the Management of Osteoporosis

OSTEOPOROSIS IS A systemic disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and increased fracture risk. The World Health Organization classifies osteoporosis by levels of bone mineral density (BMD) into normal (within 1 standard deviation [SD] of young adult men), osteopenia (low bone mass, −1 to −2.5 SD), osteoporosis (< 2.5 SD), and established osteoporosis (with 1 or more fragility fractures). Osteoporotic fractures can result from minimal trauma to a deficient skeleton and occur most commonly in the spine, wrists, and hips.

Although spine fractures are the most common, hip fractures account for the greatest morbidity and costs and have an associated 15% to 20% mortality. Common osteoporosis risk factors such as age, menopause, and thinness contribute to fracture risk, but account for only 20% to 30% of risk assessment. A low BMD is the most important risk factor, reflecting the sum of all other risks. A propensity to falls and a history of previous fractures further increase risk. Two important objectives addressed by bone density measurements are identifying persons at risk and determining treatment efficacy. The ultimate goal is primary prevention, but secondary prevention of further bone loss in at-risk persons is also relevant.

Commonly measured sites are the proximal femur, spine, calcaneus, and radius. The sensitivity for fracture prediction and the effect of disease on either trabecular or cortical bone loss dictate the choice of the site. The current techniques use x-ray transmission in either a single-energy mode limited to peripheral bones or, more commonly, a dual-energy mode for body parts with large amounts of soft tissue of varying composition. Quantitative computed tomography of the spine measures true density in a three-dimensional mode, but it is less precise and more costly.

The fracture probability is closely linked to bone density levels. A high BMD has a low risk whereas a low BMD has a high risk. Measuring BMD cannot accurately predict who will have a fracture any more than measuring blood pressure can predict who will have a stroke. The relationship of bone density to the future fracture risk, however, is stronger than that of blood pressure to stroke risk or cholesterol level to coronary artery disease risk. All measurement sites have a strong relationship to a future fracture probability, but a hip BMD has the strongest relationship to a hip fracture risk.

Because persons who should be targeted for prevention are asymptomatic, the first priority is identifying those at risk, a task suited to bone mineral densitometry. A low bone mass could be the result of either a failure to achieve adequate peak bone mass or subsequent bone loss. In either case, appropriate management can main-

tain or increase the BMD, thereby reducing the future fracture risk. Lifestyle changes and appropriate medical therapy have been shown to increase the BMD and to reduce fracture risk.

Almost all approved drugs act by reducing bone resorption. Estrogen is still the leading drug for postmenopausal women, but alendronate sodium (a biphosphonate) and calcitonin have proven efficacies. Bone densitometry results can substantially influence decisions about beginning estrogen or other drug therapy and provide follow-up to assess the effects of therapy and future fracture risk.

JOHN M.VOGEL, MD
Sacramento, California

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Collimation Approaches to 511-keV Imaging

POSITRON-EMISSION TOMOGRAPHY (PET) using fludeoxyglucose F 18 (^{18}FDG) has proved effective in evaluating patients with coronary artery disease, especially those in whom the viability of myocardial tissue is in question. The PET evaluation of the central nervous system in various disorders including dementias, stroke, and epilepsy has been well established. Recent work with PET imaging has indicated a possible role in oncology, especially in evaluating patients with melanoma, colon cancer, lung cancer, head and neck tumors, and other tumor types including lymphoma. It is capable of detecting lesions as small as 4 to 5 mm and has been shown in several studies to be more accurate and more cost-effective than computed tomography (CT) or magnetic resonance imaging in the staging of several tumor types. The major drawback to PET imaging is that it is not always available, although the supply of PET radiopharmaceutical agents, especially ^{18}FDG, is improving.

To reduce the overall cost of using PET pharmaceuticals such as ^{18}FDG, an attempt has been ongoing to use conventional Anger camera systems for detecting 511-keV annihilation radiation. Two approaches appear to be emerging using the Anger camera. One involves the use of specially designed high-energy collimators for either dual- or triple-detector systems. The other relies on coincidence-detection circuitry installed in conventional dual-detector cameras.

Several studies have demonstrated the ability to image myocardial metabolism successfully using ^{18}FDG. In one study, 15 of 57 patients were found to have mismatched defects in which the uptake of technetium Tc 99m sestamibi was reduced whereas the use of ^{18}FDG showed normal or increased activity. This pattern was associated with ischemia. Matched defects were seen in 14 patients, consistent with myocardial scarring, and 7 had both matched and mismatched defects; 21 patients had normal studies. A total of 23 patients underwent coronary angiography within three months of the dual-isotope single-photon-emission CT (SPECT) study. Coronary artery stenosis of greater than 70% was detected using dual-isotope SPECT, with a sensitivity of 100% and a specificity of 88%. It was concluded that dual-isotope SPECT using ^{18}FDG and ^{99m}Tc-sestamibi was an excellent way to identify injured or dysfunctional but viable myocardium. Works in progress have substantiated this technique, and larger studies are now ongoing.

The use of ^{18}FDG-SPECT has been compared with that of ^{18}FDG-PET imaging in patients with coronary artery disease and those with malignant tumors. In nine patients with heart disease, the ^{18}FDG-SPECT and -PET images were shown to be comparable in diagnostic information regarding the amount of viable myocardium. In seven of eight patients, malignant tissue visualized with ^{18}FDG PET was seen equally well with SPECT. Lesions not visualized with ^{18}FDG SPECT were either small (<1.5 cm) or were benign.

Several published studies have indicated the cost-effectiveness of conventional PET imaging in oncology compared with x-ray and CT approaches. The sensitivity and specificity of PET far exceed those of CT, making it cost-effective to include or exclude patients from surgical procedures using PET.

There are little published data to support the oncologic use of Anger camera-collimated systems for imaging 511-keV pharmaceuticals. The resolution for older Anger camera-collimated systems has been limited thus far by highly inefficient sodium iodide detectors for 511-keV energies. Poorly shielded systems, energy-resolution limitations for 511-keV, and resolution limitations of existing collimators were problematic. Lesions smaller than 12 mm are seldom detected. The resolution of 511-keV imaging for myocardial perfusion for assessing viability, however, appears to be good, and the technique is now clinically useful. Recent advances in camera design, including more efficient detectors, improved collimator designs, and better energy resolution have improved image quality to the point where some institutions are beginning to obtain PET-quality images with ^{18}FDG SPECT.

Anger camera detectors with coincidence-detection circuitry have recently been evaluated. Clinical trials have shown PET-quality images for oncologic applications. As instruments improve, applications will grow in oncology as well as in cardiology. Neuroimaging is competing with excellent SPECT brain imaging techniques using single-photon neuroperfusion agents. Thus, development is likely to be slower with regard to Anger camera PET radiopharmaceutical agents for brain imaging.

The feasibility of detecting tumor using the Anger camera has clearly been demonstrated, and this technique may prove useful, especially in evaluating pancreatic

masses, recurrent colon cancer, melanoma, lymphoma, head and neck tumors and other tumor types now being evaluated.

ALAN D. WAXMAN, MD
Los Angeles, California

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Detection and Localization of Gastrointestinal Bleeding

SUCCESSFUL TREATMENT of gastrointestinal bleeding depends on the accurate detection and localization of the actual bleeding site. Angiography can diagnose and possibly treat a bleeding site if the patient is actively bleeding during the examination at a rate of 1 ml or more per minute. Most patients bleed intermittently, however; therefore, angiography may fail to detect the bleeding site. Scintigraphy, on the other hand, can determine whether a patient is actively bleeding and help to localize the bleeding site. Foreknowledge of the approximate bleeding site allows an angiographer to tailor an examination, thereby decreasing the time of an examination, the amount of contrast medium required, and a patient's radiation exposure.

Two scintigraphic techniques are available for detecting lower gastrointestinal bleeding: technetium Tc 99m sulfur colloid and technetium Tc 99m-labeled erythrocyte (^{99m}Tc-RBC) scans. After 370 to 550 MBq of ^{99m}Tc-sulfur colloid is administered, flow images of the abdomen and pelvis are acquired, followed by sequential static or dynamic images for 20 minutes. The presence of intraluminal activity that increases with time and is seen to move within the bowel indicates acute gastrointestinal bleeding. ^{99m}Tc-Sulfur colloid scans can detect active bleeding rates as low as 0.05 to 0.1 ml per minute. Although the ^{99m}Tc-sulfur colloid scan is the most sensitive method for detecting gastrointestinal bleeding, it will detect hemorrhage only if the patient is actively bleeding during the brief imaging time of the study. The role of ^{99m}Tc-sulfur colloid scans is limited to cases of unstable patients bleeding acutely where rapid localization of the bleeding site before surgery or angiography is necessary or where labeling erythrocytes is not feasible.

^{99m}Tc-Labeled erythrocyte scans (740 to 915 MBq of activity) are performed by acquiring flow images, followed by sequential static or dynamic images for 60 to 90 minutes or until bleeding is confirmed. These scans demonstrate bleeding rates as low as 0.1 to 0.2 ml per minute. To detect intermittent bleeding, delayed imaging may be done as long as 24 hours after the ^{99m}Tc-RBC is administered. The recent release of a commercially available in vitro kit with a labeling efficiency of greater than 98% has improved accuracy. High labeling efficiency of the tagged erythrocytes is necessary because free sodium pertechnetate Tc 99m can simulate acute hemorrhage. Therefore, erythrocyte labeling should be done using either the in vitro kit or a routine in vitro technique. Precise static localization of the site of bleeding may be problematic with ^{99m}Tc-RBC scans because blood may move antegrade or retrograde within the bowel. The technique of dynamically viewing acquired bleeding studies in a cinematic loop has improved the accuracy of localizing bleeding sites.

A comparison imaging study was done of 100 patients with lower gastrointestinal bleeding in which a ^{99m}Tc-RBC study immediately followed the use of a ^{99m}Tc-sulfur colloid scan. The ^{99m}Tc-sulfur colloid scan detected only 4 cases of bleeding whereas the ^{99m}Tc-RBC scans found 38. The sensitivity of the ^{99m}Tc-RBC scans was 93%, specificity 95%, and accuracy 94%.

In conclusion, a cinematic ^{99m}Tc-RBC scan is the study of choice for the scintigraphic evaluation of lower gastrointestinal bleeding. Scintigraphy can be used to detect active bleeding and to localize the bleeding site before expensive and invasive procedures such as angiography and surgery are done.

RHONDA A. WYATT, MD
Fairfield, California

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ADVISORY PANEL TO THE SECTION ON NUCLEAR MEDICINE

ROBERT J. LULL, MD
Advisory Panel Chair
CMA Council on Scientific Affairs Representative
San Francisco

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Northern California Chapter
Sacramento

JOHN MILLER, MD
Society of Nuclear Medicine
Southern California Chapter
Los Angeles

was wide, and no generalizations or trends can be deduced with regard to renal biopsy, treatment, or outcome.

From these case reports, five mechanisms of HAV-induced renal failure have been proposed. First, prerenal azotemia due to hypovolemia caused by nausea, vomiting, diarrhea, and anorexia may cause a disturbance of the renal circulation with the subsequent development of acute tubular necrosis and acute renal failure.[21] Second, immune complex deposition of various types—IgG, IgA, IgM, C3, and C1q—has been documented in five cases, including the current case, and postulated in many others.[11,14,26,27] In cases confirmed by a renal biopsy,[11,14,26,27] immune complexes are accompanied by mesangial hypercellularity with varying degrees of glomerular involvement; there was no tubular immunologic involvement. Moreover, viral particle deposition has been identified in kidney specimens obtained from animals infected experimentally with HAV.[29] Third, endotoxin may be present in the circulation of patients with substantial liver impairment, even in the absence of true infection.[30,31] Endotoxin may induce renal vasoconstriction with possible deposition of fibrin and increased sympathetic tone, which may lead to acute tubular necrosis and acute renal failure. Fourth, hyperbilirubinemia may cause vasoconstriction of the renal vasculature, leading to renal failure.[32] Fifth, a direct cytopathic effect by HAV has also been proposed as a cause of acute renal failure.[6] Furthermore, it should be noted that all of the aforementioned factors may contribute to a multifactorial cause of HAV-induced renal failure.

In our evaluation of the current case of HAV-induced renal failure, we speculate that each of the aforementioned mechanisms, with the possible exception of prerenal azotemia, might have contributed to the development of transient renal failure in our patient. It is unlikely that her ibuprofen use caused the episode because of the negligible amount of ibuprofen taken and the urine Hansel stain negative for eosinophils, which are generally present in cases of drug-induced acute renal failure. Our review of this case and the relevant literature suggests that there is strong evidence to implicate HAV as a cause of—and not only an association with—acute renal failure. It remains to be elucidated why the histopathologic features are so variable in these cases of HAV-induced acute renal failure and which factors predispose a patient to have immunologic involvement versus interstitial and tubular involvement.

Finally, physicians must be aware of the spectrum of systemic involvement associated with hepatitis A, including the possibility of acute renal failure.

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Intussusception in an Adult

MARK A. MARINELLA, MD
CHRISTOPHER D. CONLEY, MD
Ann Arbor, Michigan

INTUSSUSCEPTION IS an unusual cause of abdominal pain in adult patients, accounting for only 5% to 16% of all cases.[1,2] Because of its rarity and the vagueness of its symptoms, the diagnosis may be missed or delayed. We report this case of intussusception in a man to alert clinicians to its possible occurrence and to illustrate its characteristic appearance on a computed tomographic (CT) scan.

Report of a Case

The patient, a 44-year-old man with no previous medical history, presented to the emergency department because of left periumbilical pain. The pain began three days before that, awakening him from sleep. It remained constant in the left periumbilical area without radiation. He had an episode of emesis the day before presentation, but did not have hematemesis, hematochezia, melena, fever, chills, flank pain, hematuria, dysuria, or testicular pain. He had had a normal bowel movement the morning he was seen. He had never had any previous episodes of abdominal pain and had not been taking nonsteroidal anti-inflammatory drugs.

The patient took no medication and did not smoke or consume ethanol. His temperature was 37.4°C (99.3°F), his pulse rate was 88 beats per minute, respirations were 18 per minute, and his blood pressure was 129/80 mm of mercury. The results of a general physical examination were normal. The abdomen was soft with normoactive bowel sounds and with tenderness over the left periumbilical area. There was no organomegaly, ecchymoses, distention, or peritoneal signs. His testicles were normal, as were all hernial orifices. He was nontender on rectal examination, and the stool was negative for occult blood.

Laboratory studies revealed a leukocyte count of 15×10^9 cells per liter (15,000 per mm^3), with 0.75 (75%) segmented neutrophils. Serum amylase, lipase, electrolytes, and creatinine levels were normal, as were liver function test results and a urinalysis. A plain radiograph of the abdomen showed focally dilated small bowel loops in the left side of the abdomen, but disclosed no evident obstruction, free air, cholelithiasis, pneumobilia, or nephrolithiasis.

While being prepared for a CT scan of the abdomen, the patient had increasing pain, emesis, and abdominal distention. The CT scan revealed a small mass lesion with fat attenuation in the cecum with areas of dilated small bowel, consistent with ileocecal intussusception (Figure 1). The patient had a nasogastric tube placed and received intravenous crystalloid solution. A surgical consultant examined the patient and the CT scan and recommended surgical therapy.

The patient was taken to laparotomy where an ileocecal intussusception was found without any evidence of gangrenous bowel. Several centimeters of his distal ileum, which contained a lipoma, were resected. The operation and his postoperative course were uneventful, and he was discharged five days later feeling well.

Discussion

Intussusception in an adult is a rare disorder characterized by an insidious onset and vague abdominal complaints that often eludes diagnosis. Adults may have recurrent symptoms of partial small bowel obstruction for several weeks. Other symptoms include crampy abdominal pain, nausea, emesis, abdominal distention, changes in bowel habits, and occult gastrointestinal blood loss.[1] Intussusception is much more common in children, with adult

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From the Departments of Internal Medicine (Dr Marinella) and Radiology (Dr Conley), University of Michigan Medical Center, Ann Arbor.

Reprint requests to Mark A. Marinella, MD, 33 W Rahn Rd, #201, Dayton, OH 45429.

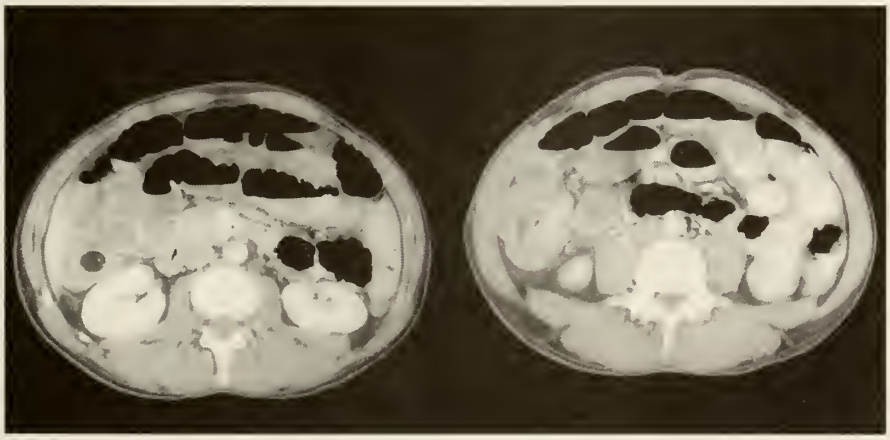

Figure 1.—An abdominal computed tomographic examination of the abdomen with oral contrast shows, in the left image, a round, 2-cm mass centrally within the distal ascending colon. There are multiple loops of dilated small bowel. In the right image, the scan, taken about 6 cm lower than the left section, shows a crescentic area of fat attenuation in the vicinity of the cecum.

cases accounting for only 5% to 16% of all cases.[1,2] An intussusception occurs by the telescopic invagination of a bowel segment and its mesentery (the intussusceptum) into the lumen of adjacent bowel (the intussuscipiens). Symptoms of bowel obstruction eventually ensue, and bowel infarction may occur due to compromise of the mesenteric blood supply.[3]

The vast majority of small bowel intussusceptions in adults are due to an underlying lesion in the bowel lumen.[1,3] The most frequently involved area is the ileum, followed by the duodenum and jejunum. Most intussusceptions arising in the small bowel are due to benign neoplasms, usually lipomas.[1,2,4] Other causes of small bowel intussusception include malignant tumors—that is, sarcomas—Meckel's diverticulum, chronic ulcers, adhesions, a heterotopic pancreas, and foreign bodies.[1,2]

Plain radiographs of the abdomen may be normal, or they may show evidence of small bowel obstruction. A barium enema study classically shows the "coiled spring" sign due to barium layering between the intussuscipiens and the intussusceptum.[4] Computed tomographic scanning may be the imaging procedure of choice, producing a characteristic finding of multiple layers of mesentery and small bowel.[2,3] According to some authors, an eccentric crescent of fat attenuation due to mesentery is the principal finding of intussusception on a CT scan.[3] This finding is demonstrated in the right-sided image in Figure 1 and is caused by the distal small bowel and its mesentery prolapsing into the cecum and proximal ascending colon. The homogeneous fat attenuation of a lipoma also contributes to the diagnosis and can be seen in the central distal ascending colon in the left-sided image of Figure 1.

The treatment of intussusception is surgical. Reducing an intussusception in an adult with the use of enemas is not an accepted mode of therapy and should not be attempted. Laparotomy with manual reduction and resection of the underlying lesion is the definitive treatment.[1,4] Some authors advocate examining frozen sections to confirm the benign nature intraoperatively.[4]

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Topics in Primary Care Medicine

Current Pharmacologic Treatment of Multiple Sclerosis Symptoms

PETER-BRIAN ANDERSSON, MBChB, BSC(MED)(HONS),DPhil, *and*
DONALD E. GOODKIN, MD, *San Francisco, California*

About 350,000 persons in the United States have multiple sclerosis, and primary care physicians are often called on to provide symptomatic therapy for these patients. We review our current pharmacologic approach to the management of multiple sclerosis exacerbations and the symptoms of spasticity, fatigue, bladder and bowel involvement, neurobehavioral complaints, pain syndromes, dystonic spasms, and tremor and ataxia.

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Multiple sclerosis is the most common cause of neurologic disability affecting young adults in the Northern Hemisphere. It is estimated that 350,000 persons in the United States are affected with this disease, and primary care physicians are often called on to provide these patients with symptomatic therapy. We review our current pharmacologic approach to the management of multiple sclerosis exacerbations and symptoms that frequently occur in otherwise clinically stable patients.* Multidisciplinary care and disease-modifying therapies, equally important topics, are reviewed elsewhere.[1,2]

Acute Exacerbations

Exacerbations of multiple sclerosis consist of the appearance of new, or worsening of old, clinical signs or symptoms that last more than 24 hours in the absence of fever or infection. Clinical deterioration in conjunction with fever or infection is considered to be a "pseudoexacerbation." Pseudoexacerbations should be considered in any patient with multiple sclerosis having acute or subacute clinical deterioration, and the source of fever or infection should be identified and treated before considering the use of glucocorticosteroids.

The use of both glucocorticosteroids[3–6] and corticotropin[5,6] reduces the intensity and duration of the neurologic disability during relapses, though the intravenous (IV) administration of 1 gram of methylprednisolone sodium succinate each day for three to five days, followed by oral prednisone therapy begun at 60 mg and tapered gradually during the subsequent 11 to 18 days, is more efficacious than the intramuscular administration of corticotropin.[5–7] Preliminary evidence suggests similar efficacy when 1 gram of methylprednisolone is administered orally, and this route of administration appears to be well tolerated.[8] There is currently no consensus as to the dose, route of administration, or duration of steroid therapy for multiple sclerosis relapses, though data for clinical benefit[3–6] exist with high doses only, and reductions in gadolinium contrast enhancement of acute plaques are dose dependent.[9] Further, there is no evidence that steroid treatment of multiple sclerosis relapses nor long-term (maintenance) steroid therapy has any effect on the ultimate course of the disease (reviewed by Myers).[10] It is our current practice to treat only acute exacerbations that result in substantial disability with 1 gram of methylprednisolone given IV for 3 days, followed by 60 mg of prednisone administered orally and the dose tapered over 11 days. Until a larger clinical experience is published, we remain reluctant to treat multiple sclerosis patients with 1 gram of oral methylprednisolone because of lingering concerns regarding toxicity.

The therapeutic benefits of glucocorticosteroids in acute exacerbations are poorly understood, but are currently postulated to be attributable to one or more of the following mechanisms of action:

- Reduced blood-brain barrier permeability and resulting tissue edema,[9,11]
- Decreased intrathecal immunoglobulin G synthesis and complement activation,[10]
- Reduced proinflammatory cytokine production,[12]
- Immunosuppression by transforming growth factor β,[13] and
- Reduced expression of adhesion molecules on vascular endothelium.[14]

Patients with a first episode of isolated optic neuritis appear to be at a reduced risk of multiple sclerosis

*See also the editorial by L. B. Krupp, MD, "Advances in the Treatment of Multiple Sclerosis," on pages 320–321 of this issue.

From the University of California, San Francisco, School of Medicine (UCSF)–Mount Zion Multiple Sclerosis Center.
Reprint requests to Donald E. Goodkin, MD, Medical Director, UCSF–Mount Zion Multiple Sclerosis Center, 1600 Divisadero St, San Francisco, CA 94115.

developing for the following two years when treated with IV methylprednisolone, 250 mg every six hours for three days, followed by a tapering course of oral prednisone. This benefit is not observed in similar patients treated with 1 mg per kg of body weight of oral prednisone for 11 days.[15] The mechanism for this apparent treatment effect is unknown, and it has been postulated that glucocorticosteroids reduce T-cell reactivity to immunogenic myelin peptides that emerge after an initial episode of demyelination.[16] It is our practice to treat monosymptomatic optic neuritis with a regimen of 1 gram of IV methylprednisolone each day for three days, followed by prednisone, 60 mg administered orally each day for six days, and the dose tapered by 10 mg per day thereafter.

Spasticity

Spasticity is characterized by a velocity-dependent increase in resistance to passive or active movement of muscles. Spasticity is generally associated with weakness, hyperreflexia, extensor plantar responses, spontaneous muscle spasms, and limb stiffness. Physical therapy—daily active and passive range-of-motion exercises—and splinting are essentials of management to limit the development of contractures.[17]

Before initiating pharmacologic therapy for spasticity, it is important to recognize that limb stiffness often provides support for ambulation. Patients with spasticity that is associated with hip flexor weakness may lose their ability to ambulate if spasticity is treated too aggressively. It is also important to consider the possibilities of subclinical urinary tract infection and bladder or bowel distention before initiating therapy because these conditions may aggravate preexisting spasticity.

We restrict the treatment of spasticity to ambulatory patients without severe hip flexor weakness, those in whom treatment will facilitate personal care (for example, turning in bed or intermittent urethral catheterization), and patients who have painful spasms. We begin therapy with baclofen, 5 mg two or three times each day, and increase this dose by 5 mg every three days as tolerated. Frequent telephone contact with the patient is helpful in titrating the dosage. Doses approximating 30 mg each day are generally well tolerated, whereas higher doses increase the likelihood of adverse symptoms such as weakness, drowsiness, and leg swelling. Many patients require and tolerate daily doses approximating 80 mg, and occasionally a patient may respond only at higher doses. Patients treated with baclofen should be monitored for possible asymptomatic elevations of aminotransferase levels, and patients with compromised renal function may require adjusted dosage. The abrupt termination of therapy has been associated with agitated behavior, paranoid ideation, and seizures. Optimal results are achieved when pharmacotherapy is coupled with muscle stretching exercises supervised by a physical or occupational therapist.[17] Supplemental oral doses of diazepam, 1 to 2 mg, or clonidine, 0.1 to 0.2 mg, administered two or three times each day are also well tolerated and may be used to advantage to potentiate the therapeutic effects of baclofen.[18] Although the use of dantrolene sodium is often effective in patients with spasticity resulting from central nervous system trauma, its benefits in patients with multiple sclerosis are almost always overshadowed by unwanted weakness and sedation.

Intrathecal baclofen administered by a subcutaneous self-contained pump represents a reasonable alternative route for patients with severe spasticity that is unresponsive to oral therapies discussed earlier. This route of administration achieves fourfold higher cerebrospinal fluid drug concentrations while using only 1% of the oral dosage generally required for a treatment effect. A review of this experience suggests that more than 95% of patients treated with intrathecal baclofen have abatement or abolition of spasticity and spasms.[19] Surgical implantation of the self-contained pump, occasional mechanical or connecting tube malfunction, and cost represent obstacles to the more widespread use of this therapeutic application.

Bladder Symptoms

About 75% of patients with multiple sclerosis have symptoms of bladder dysfunction.[20] Symptoms of urgency, frequency, and urge incontinence are generally due to detrusor spasticity, whereas hesitancy, interruption of the urinary stream, or urine retention are more frequently associated with detrusor hypotonicity and incomplete relaxation of the internal and external sphincters during detrusor contraction (sphincter dyssynergia). Distinguishing these two types of bladder dysfunction is essential when attempting to provide effective therapy.

Measuring the amount of urine voided and the postvoiding volume of urine remaining usually enables the distinction to be made between bladder spasticity and hypotonicity. It is our practice to catheterize all symptomatic patients to determine the postvoiding residual volume and to exclude the possibility of a urinary tract infection as the cause of symptoms. Patients who void volumes of less than 200 to 300 ml and who have residual volumes of less than 100 ml generally have detrusor spasticity and often will have a reduction in symptoms with anticholinergic agents. We favor the use of oxybutynin chloride in doses of 2.5 to 5.0 mg orally two to three times each day, although the administration of propantheline bromide, 15 mg orally three to four times each day, is equally effective. Both medications are well tolerated, although dryness of the mouth and constipation are commonly experienced. Patients who void volumes of greater than 500 ml and who have postvoiding volumes of more than 100 ml generally have a hypotonic detrusor muscle, and those with residual volumes in excess of 200 ml often have associated sphincter dyssynergia. These patients are often responsive to intermittent self-catheterization,[21,22] a procedure easily taught and, in our experience, more effective than administering terazosin hydrochloride, 5 mg orally three to four times each day. Clinicians who lack the

resources to teach intermittent self-catheterization techniques should consider referring symptomatic patients to a multiple sclerosis center or a urologist. We refer to a urologist all patients with recurrent urinary tract infections or incontinence that does not respond to these measures.

Bowel Symptoms

Constipation, evacuation urgency, and incontinence occur in about 50% of patients with multiple sclerosis.[23] These symptoms are associated with abnormal colonic pressures, absent postprandial colonic motility, and functional outlet obstruction during defecation by an impaired puborectal muscle and anal sphincter relaxation.[24] Dietary adjustments with regular high-fiber meals, bulk formers, laxatives, enemas, timed voidings, and digitalization of the anus often alleviate symptoms. Rectal bags are occasionally useful, and diversionary procedures are rarely if ever indicated.

Fatigue

Fatigue occurs in about 75% of patients with multiple sclerosis and is typically worse during afternoon hours and with increased ambient temperature.[25] It is distinct from the fatigue seen in depression and sleep disorders,[26] and, in contrast to fatigue in normal controls, that in patients with multiple sclerosis is overwhelming and often requires the patient to sit, lie down, or sleep. The fatigue of this disorder correlates poorly with the degree of functional impairment shown on neurologic examination.[27,28]

Drug intervention coupled with the training of energy conservation techniques is often helpful in managing this symptom.[29] Amantadine hydrochloride, given orally in dosages of 100 mg once or twice each day, is effective in 41% to 62% of patients.[26–28] Other effective medications include pemoline, 37.5 mg, or fluoxetine hydrochloride, 10 to 20 mg, administered orally once or twice each day. Anxiety and insomnia are occasional adverse side effects. There is anecdotal evidence that patients who respond to these agents do so within several days and are unlikely to respond to higher doses. A sustained response in some patients may be facilitated by treatment regimens that include one-week drug holidays every three to four weeks.

Depression and Inappropriate Expressions of Emotion

Bipolar affective disease, anxiety disorder, and depression are more common in patients with multiple sclerosis than in age- and sex-matched groups.[30–34] Whether these conditions are directly attributable to cerebral plaques or are consequences of the psychological stresses associated with multiple sclerosis are not known. Therapy for depression in patients with multiple sclerosis is similar to that for the general population. We administer amitriptyline starting at a dosage of 25 mg each evening before bed and increasing this dose by 25 mg each week to a maintenance dose of 75 to 100 mg each day. The anticholinergic properties of this drug are also helpful to patients with symptoms of bladder spasticity or chronic pain. Patients with severe fatigue tend to tolerate this drug poorly and may respond more favorably to fluoxetine, 10 to 20 mg administered orally each morning. Patients with multiple sclerosis are at increased risk for suicide compared with the age-matched general population.[35] They should be questioned directly about symptoms suggestive of depression at each medical evaluation, and those who are unresponsive to initial treatment efforts should be referred for psychiatric consultation.

Inappropriate expressions of emotion (pathologic laughter or weeping) occur in 10% of patients[33] and are generally responsive to the oral administration of amitriptyline at a dosage of 10 to 75 mg each day.[31] Anecdotal experience suggests that oral fluoxetine in dosages of 10 to 20 mg each day is equally effective.

Pain Syndromes

Pain is reported to occur in about 55% of patients with multiple sclerosis.[36] Female patients and patients older than 40 years appear to be at an increased risk. About 80% of these patients have chronic pain syndromes. These syndromes are characterized by extremity dysesthesia, back pain, leg spasms, and abdominal pain and often occur in conjunction with myelopathy.

Chronic Pain

Chronic dysesthetic extremity pain, the most common of the chronic pain syndromes, is generally characterized as a burning or raw sensation that worsens at night. Administering tricyclic antidepressants such as amitriptyline in oral dosages of 25 to 150 mg each day is partially effective in 40% to 66% of treated patients.[36,37] Regimens consisting of carbamazepine given in dosages of 100 to 200 mg orally three times each day or phenytoin, 100 mg given orally three times each day, appear to be similarly effective. Occasionally a patient will respond to transcutaneous nerve stimulation techniques and cognitive behavioral therapy in the context of a comprehensive pain management program.

Chronic lumbosacral pain is frequently associated with mechanical stress on the spine, with spasticity and weakness. Physical therapy and nonsteroidal anti-inflammatory agents are frequently of benefit. It is important to maintain vigilance for radiculopathy from disc herniation because patients with multiple sclerosis commonly have associated degenerative disc disease.[36]

Painful tonic spasms of the limbs are commonly triggered by tactile stimuli, positional change, decubitus, and urinary tract infections. Antibiotic treatment of obvious or subclinical infections is often effective. The use of baclofen in dosages similar to those required for the management of spasticity is reported to be effective therapy in about two thirds of patients.[36]

Acute Pain

The acute pain syndromes in multiple sclerosis

include trigeminal neuralgia, painful dysesthesia, Lhermitte's sign, or dystonic spasms (vide infra). Trigeminal neuralgia is more commonly bilateral (31% versus 10%) and seen at a younger age (50 versus 63.5 years),[38] but it is otherwise indistinguishable from trigeminal neuralgia occurring in patients who do not have multiple sclerosis. Each of these conditions is generally partially or completely responsive to the administration of carbamazepine, 100 to 200 mg administered orally two or three times each day.[39,40] Phenytoin, 100 to 200 mg two or three times each day,[41] and baclofen, 10 to 30 mg one to three times each day,[42] are similarly effective alternatives, and early experience with gabapentin, 300 to 400 mg three times a day, has been promising. Percutaneous trigeminal rhizotomy may be indicated for medically refractory cases.

Dystonic Spasms

Dystonic spasms or "tonic seizures" consist of paroxysmal tonic posturing that affects one or more extremities and occasionally affects one side of the face. In most patients, dystonic spasms are painful and stereotyped, spreading over the involved area over several seconds and at times crossing the midline. They may last as long as two minutes, be preceded or followed by sensory disturbances, and recur repeatedly. Frequently these spasms are triggered by hyperventilation, movement, or tactile stimulation of the limb. Some patients suggest that alcohol consumption may trigger an event. Dystonic spasms bear no relation to the degree of underlying spasticity and are differentiated from simple flexor spasms by the greater intensity of the pain, longer duration, stereotypy, the possible presence of sensory symptoms, and triggering factors. Dystonic spasms are not epileptic, do not impair consciousness, and generally respond well to the use of carbamazepine or phenytoin orally in dosages of 100 to 200 mg two to three times each day.

Tremor and Ataxia

Tremor and ataxia are among the most debilitating consequences of multiple sclerosis. These disorders are poorly responsive to pharmacotherapy. The use of clonazepam, 0.5 to 2 mg orally one to four times each day,[25] and primidone, 125 to 250 mg orally two to three times each day, is partially effective in a few patients. Occasionally a patient may be partially responsive to the administration of propranolol hydrochloride, 20 to 40 mg orally two to three times a day. Inhaled marijuana is not beneficial,[43] and isolated reports of success with other agents, including isoniazid, carbamazepine, acetazolamide, and glutethimide, have not been confirmed in practice.

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*An asterisk denotes a review of a particular symptom.

This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the series' editors.

STEPHEN J. McPHEE, MD
TERRIE MENDELSON, MD
Assistant Editors

Editorials

A Primer for Clinicians on Mushroom Poisoning in the West

THE HISTORY OF mushrooms is surrounded by much mystery and superstition. This mystique is perhaps most commonly associated with the mushroom's poisonous reputation. Most mushroom species, however, are not poisonous; of the 5,000 known species of mushrooms, fewer than 100 are poisonous to humans. Poisonous mushrooms have no characteristic smell or taste and often resemble edible mushrooms. Cooking seldom destroys the deadly toxins. This poses a possibly lethal risk for novice enthusiasts of mushroom hunting.

Hunting and consuming of wild mushrooms have become increasingly popular, an epicurean delight for some, and for others, a means of subsistence. Unfortunately, errors in identification lead to many thousands of reported poisonings all over the world each year. Almost 10,000 mushroom exposures are reported annually to the American Association of Poison Control Centers, representing just under 1% of their calls.[1] Whereas severe mushroom poisonings fortunately are rare, about 100 to 200 fatalities per year due to mushroom poisoning occur in the United States and Europe. Moreover, 90% to 95% of deaths are caused by a single species, *Amanita phalloides*. This species is reported with increasing frequency in this country, especially along the West Coast.[2]

The prevention of mushroom poisoning by increased knowledge continues to be a reasonable goal. With caution, collecting and cooking wild mushrooms is relatively safe. Unfortunately, edible and nonedible mushrooms are frequently misidentified by mushroom collectors. As the saying goes, "There are old mushroom hunters and bold mushroom hunters, but there are no old, bold mushroom hunters." Thus, more emphasis on public education through service announcements could be warranted and cost effective if directed at appropriately targeted groups and at appropriate times of the year. The article in this issue by Jeffrey Jacobs, MD, MPH; Julie Von Behren, MPH; and Richard Kreutzer, MD, "Serious Mushroom Poisonings in California Requiring Hospital Admission, 1990 Through 1994," provides from their database some of this needed demographic targeting.[3]

One of the most interesting findings in this report is the increased incidence of hospitalization for mushroom poisoning in children younger than 5 years. This point certainly behooves parents to teach small children not to eat any mushroom they come across. Jacobs and coworkers report that certain counties in California, such as Los Angeles, Riverside, San Bernardino, Orange, San Diego, Santa Clara, and Fresno, have the most hospital admissions and that Humboldt, Merced, Yolo, Riverside, Fresno, Marin, and San Luis Obispo counties have the highest incidence. They also note that there is an increased incidence of poisoning in the months July through October. These geographic locations and times of year reflect not only natural growth patterns of mushrooms, but probably also the increased incidence of mushroom collecting because of the higher population concentrations in these locations and an increased focus on the out-of-doors during these months. We could conclude that educational efforts for poisoning prevention in California should occur beginning in the summer and in the above-mentioned counties. Mushroom collectors should know how to identify mushrooms with absolute certainty, and if there is even the slightest concern, leave it there!

If there is any problem in the methods of their study, it would be under identification of cases of serious mushroom poisoning because of incorrect diagnostic coding. Death due to mushroom poisoning may be hidden because fatalities may be recorded as hepatic failure, increased intracranial pressure, and the like. Also, the species involved unfortunately could not be determined from their database.

Because the total prevention of mushroom poisonings is a goal likely never to be reached, it is important for clinicians to focus on diagnosis and treatment. The differential diagnosis of mushroom poisoning includes food poisoning, gastroenteritis, infectious colitis, acetaminophen overdose, carbon tetrachloride ingestion, psychosomatic symptoms, or psychoses. As with any clinical problem, the diagnosis of mushroom poisoning must at least be considered in a patient with the appropriate symptoms.

Based on the classification of toxin and clinical symptoms, there are different types of mushroom poisoning, including syndromes caused by *A phalloides, Cortinarius orellanus, Gyromitra* species, *Amanita muscaria, Amanita pantherina*, psilocybin, gastrointestinal mushroom, *Coprinus quadrifidus*, and *Paxillus involutus*. Poisonings caused by *A phalloides, C orellanus*, or *Gyromitra* or *Paxillus* species are generally serious and often require intensive care treatment. Considerable differences in symptoms may be seen with the various mushroom species due to seasonal and location variance in the toxin content, variance in oral bioavailability, differences in metabolic activation, and differences in toxin susceptibility.[4] In general, these symptoms can include nausea, vomiting, abdominal cramping, diarrhea, chills, thirst, oliguria or anuria, weakness, dizziness, diaphoresis, hyperthermia, muscarinic symptoms, vertigo, bradycardia, hypotension, headache, euphoria, disorientation, hallucinations, and seizures.

Most patients present with gastrointestinal symptoms. It is important to establish the latency period of symptoms after ingestion as this can help determine which of the various syndromes are most likely. For example, of all fatal mushroom poisonings, 90% to 95% are attributable to *A phalloides*, with symptoms that range from those of gastroenteritis to fulminant hepatic failure. Symptoms of gastroenteritis begin 6 to 24 hours after the initial ingestion of the mushroom, characterized by severe, crampy abdomi-

nal pain; nausea; vomiting; and watery diarrhea. Hepatic failure can be seen as early as 48 hours after ingestion. In fatal cases, death occurs 6 to 16 days after ingestion.

The diagnosis of mushroom poisoning is based on careful history taking primarily, the identification of leftover mushrooms, chemical analyses, or both. It is important to elicit the first onset of symptoms and any symptoms that others who shared in the ingestion might have had. If possible, it is helpful to know the species involved, including the amount and type of preparation.

Toxins from mushroom remnants can be identified by chemical analysis using thin-layer chromatography, high-performance liquid chromatography, or gas chromatography and mass spectrometry. In those patients with suspected *A phalloides* poisoning, body fluids can be analyzed for α-amanitine by a recently developed radioimmunoassay.[4] Measuring alkaline phosphatase isoenzyme levels may be helpful. Unfortunately, positive identification is often not made; in less than 5% of the cases is the mushroom species actually identified.[1] Whether positively identified or not, when a clinician suspects the presence of mushroom poisoning, he or she should contact the local poison control center. The poison control center staff can provide much-needed, appropriate, and detailed information on treatment.

The initial laboratory evaluation should include prothrombin time, platelet count, complete blood count, blood gas, and serum glucose, electrolytes, phosphate, creatinine, urea, alanine and aspartate aminotransferase, lactate dehydrogenase, and alkaline phosphatase levels. If available, factor analysis, fibrinogen, and lactate levels may be helpful.

Because of the possible development of fulminant hepatic failure, clinicians must be watchful for rising hepatic enzyme levels, especially in those patients with *A phalloides* poisoning. Throughout the patient's course, basic laboratory measurements should be observed at selected intervals and even as long as a few months after the event.

Appropriate routine treatment includes hydration and electrolyte replacement, primary and secondary detoxification, and sometimes specific antidotes. For example, specific therapy for *A phalloides* ingestion includes the administration of silibinin and penicillin G. Because delay following ingestion until treatment is common, the efficacy of both primary and secondary detoxification is limited. Nevertheless, induced emesis and gastric lavage are indicated. Because of extensive enterohepatic circulation of α-amanitine and other toxins, the repeated administration of activated charcoal is recommended. Secondary detoxification with forced diuresis and saline catharsis is also indicated. Hemodialysis and plasmapheresis are less efficient. Supportive measures can include oxygen, cardiac monitoring, and the administration of atropine sulfate if muscarinic effects are present.

If the patient progresses to hepatic dysfunction, digestive tract decontamination, the repletion of clotting factors, and protein intake restriction are appropriate initial steps. In patients exhibiting hepatic dysfunction, immediate consultation with a hepatologist and preferably with a liver transplantation unit is mandatory. In the most serious cases, early transfer to a liver transplantation center is important to identify appropriate candidates and to begin the search for a donor organ. Liver transplantation offers definitive therapy for selected severely poisoned patients. In addition, auxiliary transplantation has been recently shown in a few cases to be an excellent option because this transplant can be removed and the patient taken off immunosuppression after the native liver regenerates. A poor outcome is more likely if the decision for liver transplantation is delayed too long.

On the other hand, we certainly would not wish to pursue this form of therapy for patients who would recover spontaneously. Reasonable prognostic indicators are available from somewhat limited data, and criteria for indications of liver transplantation have been developed. Indications for transplantation include primarily a markedly prolonged prothrombin time that is only partially correctable and a constellation of findings that can include metabolic acidosis, hypoglycemia, hypofibrinogenemia, reduced factor levels, and an increased serum ammonia level following a pronounced elevation in serum aminotransferase levels. Clinicians should not wait for hepatic failure to advance to hepatic encephalopathy, azotemia, or jaundice.[5]

In summary, the article by Jacobs and colleagues helps to emphasize important points about mushroom poisoning, including prevention, diagnosis, and treatment. Mortality from mushroom poisoning has decreased in recent decades due to the vast improvements in critical care treatment, poison control center information, and the availability of liver transplantation. Historically, *A phalloides* syndrome has carried a mortality of greater than 50%, but with improved treatment in recent years, this has dropped to less than 20%. The cases of the five patients mentioned in the introduction to this article demonstrate the wide spectrum of outcomes of mushroom poisonings, with three recovering in a few days, one requiring liver transplantation, and one dying without appropriate therapy.[3]

C. WRIGHT PINSON, MD, MBA
ANNE L. BRADLEY, MD
Division of Hepatobiliary Surgery and Liver Transplantation
Department of Surgery
Vanderbilt University Medical Center
Oxford House, Suite 801
Nashville, TN 37232-4753

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Advances in the Treatment of Multiple Sclerosis

IN THE PAST DECADE there has been a dramatic evolution in the treatment and management of multiple sclerosis. In the past, the major management issue for clinicians was whether "to tell or not to tell the patient" (the diagnosis). Now clinicians and patients are asking, "With which drug therapy do we start and when?"

Both scientific and technical advances have contributed to this change. Through studies of immunopathogenic mechanisms, we have enhanced our understanding of the role of activated T cells, proinflammatory and anti-inflammatory cytokines, and interactions between T-cell receptors, antigen-presenting cells, and major histocompatibility structures (trimolecular complex). This has led to new treatment approaches targeted to specific pathogenic mechanisms. These include T-cell vaccination, monoclonal antibodies directed at the trimolecular complex, and immune modulators such as the interferons or roquinimex, a drug with effects on diverse immune cell populations. Magnetic resonance imaging has added substantially to the understanding of multiple sclerosis disease activity and provides a marker of disease progression.

As of this writing, there are two Food and Drug Administration (FDA)–approved drugs available for patients with relapsing multiple sclerosis. Both are interferon betas.[1,2] The first product, Betaseron, produced by Berlex, became available in 1993. By the spring of 1996, Avonex, produced by Biogen, was also approved. In September 1996, the advisory panel for the FDA reviewed a phase III clinical trial with copolymer 1 and recommended approval.[3] Thus, by 1997 it is probable that at least three drugs will be on the market in the United States designed to alter the natural history of multiple sclerosis.

With so many new and exciting developments, investigators and clinicians tend to focus on disease prevention. Consensus panels have met to discuss which medications will decrease the likelihood of relapse, yet not produce adverse side effects; which will slow progression; and which patients are most suitable to begin therapy.[4] While there is great interest in altering the disease course, patients also need help in dealing with the daily obstacles multiple sclerosis presents to functional activities and quality of life. The review by Drs Andersson and Goodkin elsewhere in this issue addresses this need.[5]

Multiple sclerosis is exceptionally clinically variable. Patients' symptoms range from cognitive loss to urinary incontinence. Daily issues include how to combat stiffness, weakness, painful spasms, fatigue, mood swings, and depression.

Drs Andersson and Goodkin summarize the major pharmacologic treatments available for the amelioration of multiple sclerosis symptoms.[5] Their review also highlights important changes that have occurred in the management approach to this disease. A major advance in patient management is that at most multiple sclerosis centers, patients are cared for by a team of physicians, nurses, physical and occupational therapists, and social workers. This integrated approach enhances function and quality of life. A second issue concerns the assessment of quality of life. Instruments are being developed and tested to measure quality-of-life changes as an important end point for clinical trials.[6]

Physical therapy and exercise are effective means of combatting spasticity. Medication is also often necessary. New pharmacologic therapies for this problem include the intrathecal administration of baclofen and the oral agent tizanidine hydrochloride. Tizanidine, which is shortly expected to receive FDA approval, acts as an agonist at noradrenergic receptors (differing from the mechanism of action of baclofen, which is at the γ-aminobutyric acid receptor) and has been shown to be effective for spasticity in multicenter trials in North America and in Europe.[7,8]

Patients with multiple sclerosis frequently experience problems related to bladder and bowel dysfunction. These include both the failure to store and the failure to empty. In the case of bladder dysfunction, intermittent catheterization, as the authors point out, can give patients what they want most, a sense of control over their lives.

Fatigue is another incapacitating symptom in multiple sclerosis. It interferes with patients' activities of daily living, is a frequent reason for applying for disability, and cannot easily be pigeonholed as depression or weakness. It is difficult to treat, but as reviewed in this issue, the administration of amantadine hydrochloride may sometimes help. Recently aerobic exercise was shown to help multiple sclerosis patients with spasticity and fatigue and to increase patients' sense of well-being. A gradual, individually tailored exercise program and physical therapy should be incorporated into any treatment program for fatigue and spasticity.[9]

Psychiatric symptoms and, in particular, depression are common problems. Multiple sclerosis patients are at a substantially greater risk for suicide than the general population. The early recognition and treatment of depression, anxiety, and bipolar illness can reduce symptoms of pain, fatigue, and decreased disability and open up treatment options (such as with an interferon β) that would otherwise be contraindicated.

One of the current myths about multiple sclerosis is that it is not associated with pain. Pain is frequent, however, and can occur as painful spasms, trigeminal neuralgia, aching, burning shocklike sensations, itching, and tightness. The appropriate treatment of acute and chronic pain syndromes not only lessens pain but can have added effects of enhancing mood and reducing fatigue.

The decade of the brain has proved an especially exciting time for those involved in the care of multiple sclerosis patients. Treatment strategies for enhancing quality of life, modifying symptoms, and altering the natural history of the disease are being actively pursued by clinical investigators, pharmaceutical companies, and national funding agencies. The future for patients with this disease has brightened.

LAUREN B. KRUPP, MD
Department of Neurology
State University of New York at Stony Brook

School of Medicine
HSC T-12-020
Stony Brook, NY 11794-8121

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Correspondence

Itraconazole-Related Amaurosis and Vomiting Due to Digoxin Toxicity

To the Editor: The antifungal drug itraconazole is indicated in the treatment of aspergillosis, histoplasmosis, and blastomycosis but has been used to treat other mycoses. The coadministration of other drugs such as histamine H_2 blockers, 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors, warfarin sodium, sulfonylureas, phenytoin, carbamazepine, isoniazid, rifampin, cisapride, tacrolimus, cyclosporine, astemizole, terfenadine, and triazolam can lead to hazardous drug-drug interactions. We have recently encountered a little-appreciated interaction between itraconazole and digoxin.

Report of a Case

Four months after coronary artery bypass grafting, a 67-year-old man noted midback pain. Magnetic resonance imaging of the thoracic spine and computed tomography of the chest revealed diskitis and osteomyelitis at T-7 and T-8, accompanied by a large paravertebral abscess. Fine-needle aspiration of the abscess grew *Candida tropicalis*, which was resistant to fluconazole but sensitive to amphotericin B and itraconazole. Pending sensitivity studies, the patient was treated with the intravenous administration of amphotericin B, 40 mg a day. By the fourth dose, the blood urea nitrogen (BUN) level had risen to 12.5 mmol per liter (35 mg per dl) and the creatinine level to 265 μmol per liter (3.0 mg per dl), and amphotericin B was discontinued, along with digoxin, amiodarone, and glyburide. He was discharged when the BUN level was 4.1 mmol per liter (11.5 mg per dl) and the creatinine level was 130 μmol per liter (1.5 mg per dl) while he was taking his usual medications and itraconazole, 200 mg twice a day.

Ten days later, the patient was readmitted to the hospital because of nausea, vomiting, and a grayish blurring of his vision. His heart rate was 48 beats per minute. The BUN level was 23.5 mmol per liter (66 mg per dl) and the creatinine 220 μmol per liter (2.5 mg per dl) while the serum digoxin level was 8.4 nmol per liter (6.6 ng per ml). Six vials of digoxin immune Fab were administered intravenously. Within 24 hours, the nausea and vomiting resolved, and his vision returned to normal. Azotemia was considered responsible for the digoxin toxicity, and he was discharged on reduced doses of digoxin, amiodarone, glyburide, and itraconazole, 200 mg twice a day. A week later, he was again admitted to the hospital with nausea and blurred vision. His heart rate was 53 beats per minute, and the serum digoxin concentration was 6.1 nmol per liter (4.8 ng per ml). Three vials of digoxin immune Fab were administered intravenously, and within 12 hours the nausea and amaurosis were gone. Itraconazole therapy was discontinued, and the patient received amphotericin B lipid complex without further digoxin toxicity or azotemia. The *C tropicalis* infection was clinically eradicated.

Discussion

Itraconazole-digoxin drug interaction was first described by Rex.[1] Subsequently, three other cases have been reported in detail.[2-4] Sachs and co-workers indicated that itraconazole use substantially increased the half-life of digoxin, necessitating a 60% to 75% reduction in digoxin dosing.[2] A decrease in the rate of digoxin clearance may be responsible for the elevated digoxin levels with itraconazole use. Because itraconazole has no appreciable effect on hepatic microsomal enzymes[5] and the nonrenal clearance of digoxin makes up about 30% of total clearance,[6] it seems unlikely that the inhibition of digoxin biodegradation increased the drug's half-life to the extent noted in these patients.[2]

Of the five reported cases of digoxin toxicity due to itraconazole use, all were in men with a mean age of 72 years. Four of five described visual problems, including xanthopsia, a gray haze, scotomata, and amaurosis, that occurred 7 to 13 days after starting the itraconazole regimen. Because nausea and vomiting can result from the use of itraconazole, the presence of visual symptoms should suggest digoxin toxicity in a patient receiving both drugs.

In our patient, digoxin immune Fab therapy promptly reversed the symptoms of digoxin toxicity.

LAWRENCE A. CONE, MD, DSc
RONALD B. HIMELMAN, MD
JOEL N. HIRSCHBERG, MD
JOSEPH W. HUTCHESON, RN
Department of Medicine
Eisenhower Medical Center

3900 Bob Hope Dr, Ste 308
Rancho Mirage, CA 92270

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Isoniazid-Related Fatal Hepatitis

To the Editor: The recent article by Millard and colleagues on fatal isoniazid hepatitis (June 1996 issue) was a thorough survey of all cases of death reportedly due to isoniazid chemoprophylaxis.[1] They used data from the Public Health Service to assess the death rate attributed to isoniazid, which they estimated to be 4.2 per 100,000 people started on therapy since 1972 and 1.7 per 100,000 treated since the current monitoring guidelines were established.[2] This is the most accurate estimate we have to date for the magnitude of risk for fatal isoniazid hepatitis, which is substantially lower than was previously thought.[3] The death rate that they found for monitored prophylaxis is similar to that seen in a previous study and is equivalent to the rate for death due to hepatitis of any cause in the general population.[4,5]

A major error made in this study was the use of the number of people completing therapy as the denominator for all the deaths found to calculate their risk of death, which was estimated to be as high as 7 per 100,000. A review of each of the deaths indicated that essentially all had occurred during the course of treatment or within days of discontinuing the drug before completing therapy. It is clear that those people who successfully finish a full course of treatment and survive have no further risk for drug-related death. Any figures used in this article describing their risk for death should be ignored.

SHELLEY R. SALPETER, MD
Division of Primary Care
Department of Medicine
Santa Clara Valley Health Center
750 S Bascom Ave
San Jose, CA 95128

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* * *

Drs Millard and Wilcosky Respond

To the Editor: Fatal hepatitis from isoniazid administered as a single agent for the prevention of tuberculosis is a rare event. The debate about just how rare has continued since the first reports of death from isoniazid-associated hepatitis in the early 1970s.[1] Although our study provides the best evidence to date concerning the case rate of fatal isoniazid-associated hepatitis among public sector patients, it has a number of limitations with regard to both the numerator (incomplete ascertainment of cases and possible misclassification of cause of death) and denominator. Ideally, the death rate would be expressed in terms of the number of deaths per person-time of isoniazid administration (for example, deaths per 100,000 person-months); unfortunately, only estimates of the total number of patients starting and completing therapy are available.[2] Dr Salpeter correctly points out that people who have completed therapy are no longer at risk of isoniazid-associated hepatitis. Likewise, people who have stopped taking isoniazid before completing their course of therapy are no longer at risk. For this reason, we calculated two rates: the death rate per 100,000 persons beginning therapy (an underestimate) and the death rate per 100,000 persons completely therapy (an overestimate). Recognizing the uncertainties in our data, we think that the "right" rate lies between 4.2 per 100,000 persons beginning therapy and 7.0 per 100,000 persons completing therapy.

PETER S. MILLARD, MD, PhD
Family Practice Residency Program
Eastern Maine Medical Center
417 State St, Ste 100
Bangor, ME 04401-6600

TIMOTHY C. WILCOSKY, PhD
Epidemiologic and Medical Studies Program
Research Triangle Institute
Research Triangle Park, NC 27709

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Lessons From the Practice

Nursing and Doctoring

ERIKA GOLDSTEIN, MD, MPH, *Seattle, Washington*

Lunch time; clinic is finished for the morning. I settle down in my office and turn my attention to my other job—that of a nursing mother. Taking the time out to pump breast milk in the middle of a busy day has been something of a mixed blessing. As always, my thoughts start to wander.

When I first returned to work after maternity leave, it was like having Amelia there with me. I would turn off my pager, get a glass of water, arrange pictures of Amelia over my desk, and settle down to pump. Early on, it would take close to an hour, and I repeated the process in the late afternoon. I would call her dad to ask exactly how much she was drinking and try to match her ounce for ounce. I didn't try to get any work done or answer phone calls. I just thought about the baby and all the changes she had brought into our life.

My second month back, I attended on the wards, and the experience of being a "pumping mother" underwent the first evolutionary change. I was always rushing that month. I began to eat lunch in my office while I pumped. Often I met with the senior resident, a woman, to review our patients or discuss some particular teaching or patient care issue. I no longer turned off my pager or my phone. With all the interruptions, it took an hour and a half or more, often twice a day. I gave up on my self-imposed goal of matching Amelia's daily intake.

This hectic pace continued when my month of attending ended. While I pumped, I answered pages and telephone calls, read my mail, and slowly made my way through the stack of journals that had been accumulating since the later months of pregnancy. Pumping was no longer a relaxed special time of connection with Amelia. It was a frustrating inconvenience. I hardly looked at her pictures or even thought about her.

In the past few months, the experience has evolved further. I have gone back to letting the answering machine take the phone calls. I again look at Amelia's pictures and often call home to see if I can get her to gurgle and giggle and "da-da-da" to me on the phone. The milk flows more easily, and I only pump once a day. I realize that it won't be much longer before I stop pumping all together, and soon she will wean herself completely. I want to enjoy this strange limbo time at work while I can, this powerful physical connection that intrudes on my workday. I cherish this special time to think about Amelia and about my family.

Although I don't believe that a woman can only have a place in the world by having a child, becoming a mother has brought me a new kind of balance and calm, a "rightness" that wasn't there before. Since the baby was born, I feel like a better doctor. I am calmer and more focused. I feel more connected to my patients. Almost every patient of mine, at some point in every clinic visit, will ask, "How's that baby?" and many ask to see pictures. Twice Amelia went with me to visit an elderly patient during her hospital stay, visits the patient insists did more to help get her home than "all those tests and pills."

I also feel like a better teacher. It is as though I am a better listener for students and residents. At the same time, I feel less responsible for them. I realize that I had been dealing with the residents and students as if they were my children. Now I can be supportive of them and nurturing, but in a more reasonable and ultimately more helpful way. For the women students and residents, I sense that my having a child is somehow reassuring to them as they look ahead to their own careers.

The physical nature of the experience of being pregnant and nursing a child has also brought changes in my perspective. It has made me more conscious of the physical and the emotional dimensions of my life. Physicians, with our special relationship to and knowledge of the body, have a paradoxical tendency to become removed from humanity, from being "like other people." To some extent, distancing ourselves and controlling our emotions are necessary for us to function as physicians. We must do this to be objective and effective clinicians for our patients. Yet, all too often it becomes a habit of the soul. We become distanced from ourselves, from our emotions, and from our bodies. In part, this may be what makes us such bad patients.

This need to step back from our feelings may be further accentuated in the world of academic medicine. Ensconced in our "ivory towers," we often aren't part of a community in the same way many practicing physicians are and may become even further removed from the world our patients inhabit. Being a parent has somehow brought me closer to the world of my patients.

I find myself wondering how my experience of being a mother is different from my male colleagues' experience

(Goldstein E: Nursing and doctoring. West J Med 1996; 165:324-325)

From the Department of Medicine, University of Washington School of Medicine, Seattle.
Reprint requests to Erika Goldstein, MD, MPH, Division of General Internal Medicine, Harborview Medical Center, Box 359780, 325 Ninth Ave, Seattle, WA 98104.

of being fathers. Until now, I never thought of myself as a "woman in medicine," but with these life changes, I have become aware of differences between us. I wonder how much of a role the physical experiences play, or whether the time I set aside for pumping and the activity itself in the middle of a busy workday allow me to be more aware of emotional connections. Although I know that many of my male colleagues are trying to strike a new kind of balance between work and home, I don't know how they think of their families in relation to their work.

I know that my experience is different from that of the senior male physicians with whom I work in my academic medical center, but I'm not sure how much of this is a generational difference. In conversations with several of them, it has been clear to me that, for them, parenting has been different. They have mentioned missing out on watching their own children grow up or have commented on how differently I and my younger colleagues (both men and women) work at balancing our work and our family lives. These are people of integrity whom I admire and respect. They are professional role models for me in their values and their dedication. Yet, they are not life role models, and although I have found one or two such models in other institutions, examples of people who successfully balance work and home life are rare. Frank discussions of these issues are equally rare. The absence of these discussions and successful examples is disquieting.

Now that I'm done pumping for today, have put the bag of milk into the cooler, and am getting ready to go back to work, I realize that I'm going to miss this special time and the opportunity to reflect on all these things. I hope I remember to look up at Amelia's beautiful face during my busy day and to call home to hear her babble, even after I no longer have this physical connection. I hope I continue to put her first, to make the time for her in the busy days and weeks. I still don't know what motherhood will mean for my life in academic medicine. I worry about being able to strike a reasonable balance. But it certainly seems worth trying.

Acknowledgment

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Lessons From the Practice

Relations

NATHANIEL H. ROBIN, MD, *Cleveland, Ohio*

To those not involved in it, molecular genetic research must seem far removed from the patients who have the disease being studied. But that is not the case. After all, the DNA being studied in these laboratories comes from patients and their families. Clinical geneticists are the doctors with the best rapport with the families and the ones who coordinate the process of getting the necessary blood specimens. This can be an easy task, involving no more than drawing a patient's blood at the next visit and sending the specimen to the appropriate laboratory. But large families are not always willing to travel to a center to donate a blood specimen. So, the clinical geneticist often will be the one to obtain specimens for the researcher.

I had come to care for a family with a rare birth defect, one that caused their hands to be malformed and almost useless. The extended family was large, with a great many affected persons. Immediately I recognized that a family this large would be valuable to researchers studying this disorder. I contacted one such colleague, a scientist at my own institution. She said she was eager to study this family at the DNA level. "This is perfect for my work. Get the whole family, if you can," she said. She went on to tell me what information I would need to get from the family members and what kind of blood specimens. But as we spoke, I warned her, "I'm not sure they'll all be willing to go along with this. I haven't called yet."

"Oh, I'm sure they will," she said with the certainty of a researcher who never dealt with patients. "Why wouldn't they?"

Soon after, I began to contact the various branches of the family, and quickly I learned much more about this family than I cared to know. Apparently one part of the family was not on speaking terms with the rest. As soon as I would mention my young patient's name, I was hung up on at best or received a hostile diatribe at worst. Fortunately, a large part of the family was willing to speak to me.

"Mrs Pearl (not her real name), the reason we'd like to come visit you and your family is that the condition that runs in your extended family seems to be different from anything that has been described before."

"Really? The doctors here said they'd seen it before."

"Well, they are probably referring to the general type of hand abnormality, which is fairly common," I said, thinking that their local physicians didn't realize how rare this family's problem was. "But the specific hand finding in your family is very unusual."

"OK, doctor, I'll be willing to have you come and see me and my children. . . ."

All told, some 12 affected and 8 unaffected family members consented to let me into their homes, examine them, and draw their blood. Like Mrs Pearl, most were surprised that I would want to bother to do this: "The doctors up here, they said they'd seen this before."

No one I knew had ever heard of the town where they lived, but I was able to find it on a map. I traced the route from the highway to major roads, to small roads, and then to roads designated as "local" on the map. These "local" roads made up most of the trip. With my camera, tape measure, blood drawing supplies, and my carefully constructed schedule of whom I would visit when, I left with my assistant for our adventure.

We found our way with surprisingly little difficulty, passing through rural areas that we would never have seen otherwise—farm country, abandoned mills, nuclear reactors. Eventually we made our way to the town. It resembled something from a John Steinbeck novel. Small and old, with abandoned factories and rundown houses at its fringes, the town sat in the shadow of a mountain of coal to the north and a huge, long-abandoned factory to the east. My assistant, a medical school–bound undergraduate with superior motivation and an overactive imagination, expressed an anxious premonition, one that I shared as we drove around town. "This is *Deliverance*. . . . No one will ever find us. . . . We're gonna die."

But once we got into town, past the mammoth burnt-out factory and abandoned railroad cars, it wasn't so bad. Downtown was a quiet street, cluttered with memorials to veterans from every war since "The Great Conflict Between the States." And the people were friendly, although they were surprised when we asked for directions. "No one comes here from the City."

With their directions, we found the right street with little trouble. And although we were a bit nervous at first, we were well received at every house we visited. On the way, I had been a bit worried because of the one part of the family that had vehemently refused to participate.

(Robin NH: Relations. West J Med 1996; 165:326-327)

From the Departments of Genetics and Pediatrics, Case Western Reserve University School of Medicine, and the Center for Human Genetics, University Hospitals of Cleveland, Ohio.

Reprint requests to Nathaniel H. Robin, MD, Center for Human Genetics, Lakeside 1500, 11100 Euclid Ave, Cleveland OH 44106.

When I asked if I could stop by they declined, using words like "attack dogs" and "hunting rifle." So, even though the rest of the family had agreed, I retained a bit of self-preservation–motivated caution as the day began. But as everyone was nice and cooperative, I forgot my fears. Taking photographs, examining, and blood drawing proceeded without any difficulty, and by day's end, I had seen and examined all 12 affected family members and drawn their blood and seen 8 more unaffected members of the family. I also was privileged to some touching family history. One great-grandfather was very religious and strict. "He married my mother, who was affected and whose hands had been operated on in Italy. My three older brothers were born normal, but when I was born, he told her, 'God made the child this way. It is His will.' So I never had any surgery. He wouldn't let me."

Indeed, her hands were unrepaired, but she had worked her whole life. She had raised five children, all of whom, she said, she made sure received the best surgical management that they could find for their hands. This ostracized her from her siblings, especially the two brothers and one sister who had been born after and were also affected. Their father had denied those youngest siblings surgery as well. But unlike their older sister, who never let it hold her back, the youngest ones allowed their hand abnormality to be a disability. "They used this as an excuse," she told me, holding up her malformed hands. "My brothers and sister, they never worked. They don't care about nothing except themselves, just collecting disability and drinking. That's why they didn't want to see you. That, and they don't want to have anything to do with me. Once you contacted me, you signed on with the enemy as far as they were concerned."

The long day came to an end at the seventh house. Perched on top of a ridge overlooking the town, it reminded me of the home the "Beverly Hillbillies" left after Jed struck oil. I saw the last few people in this two-room house, sitting in the small main room crowded with worn couches that faced a brand-new big-screen TV.

Tired and anxious to start the long trek home, I forgot my sunglasses on top of that TV. Aside from that, the day was a resounding success. As we set off with rolls of film, pages of notes, and dozens of tubes of blood, my assistant and I could hardly believe how well things had gone.

The next morning, I began to review the data that I had generated, transcribing my cryptic notes immediately so as not to lose the details. I also began contacting the various local physicians who had taken care of the different family members, trying to get old records or at least verbal reports of procedures done years ago.

After a series of secretaries and nurses, I finally reached one of the physicians. "Doctor, I'm calling about a few members of a family that is participating in a study here at the medical center. You and some of your colleagues cared for them some years ago." I went on to describe the hand anomalies to him, figuring that he would not have forgotten such an unusual case. "This condition is exceptionally rare, and they've agreed to participate in a study aimed toward describing their disorder at a clinical and molecular level."

"Neat. What can I do to help?"

"Well, I need some information about what was seen during surgery."

"Sure thing. Let me pull their charts. Now, what's the family's name?"

"It's not one name. The kids are Melani Pearl, Alex Herrera, and Jason David Elstern."

"Sure, hold on a bit. Jeannie. . . ." The phone went silent, followed by the comforting sound of Barry Manilow, the universal indication of being put on hold.

Suddenly Barry stopped. "Let's see, . . . Pearl. I operated on her, and my partner did the other two. They had that odd deformity of the . . . Wait. You mean they're related?"

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
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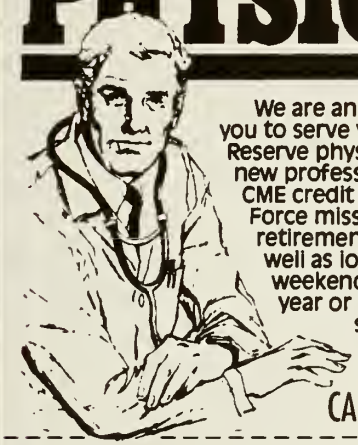

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Hawaii Medical Association
1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 18-20, 1996, Kauai Marriott, Lihue.

Idaho Medical Association
305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 23-26, 1997, Sun Valley Inn, Sun Valley.

Nevada State Medical Association
3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 1-4, 1997, Sheraton El Conquistador Hotel, Tuscon, AZ.

New Mexico Medical Society
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PFIZER 265

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www.wjmed.com 332

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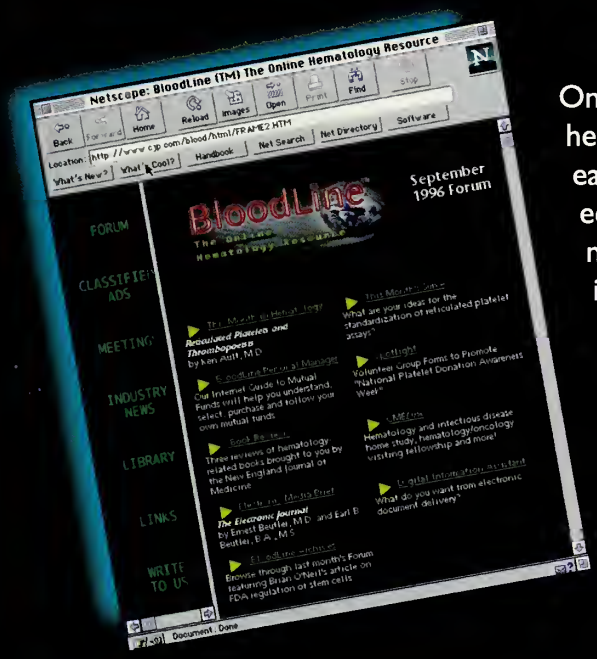

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The Western Journal of Medicine

VOLUME 165 • NUMBER 6 DECEMBER 1996

ARTICLES

349 Onychomychosis—New Therapies for an Old Disease
A K GUPTA, R K SHER, P DE DONCKER, D N SAUDER, and N H SHEAR

352 Avoiding Medication Mixups—Identifiable Imprint Codes
P VASUDEVAN, T DEL GIANNI, and W O ROBERTSON

CONFERENCES AND REVIEWS

355 Lung Transplantation—Part I. Indications and Operative Management
D E WOOD and G RAGHU

364 Myocardial Viability
Y BIRNBAUM and R A KLONER

EPITOMES

372 Important Advances in Obstetrics and Gynecology

ALERTS, NOTICES, AND CASE REPORTS

379 Ruptured Sinus of Valsalva Aneurysm in a Patient With Autosomal Dominant Polycystic Kidney Disease
R F SPRUNG, R M CATALDO, M C GREGORY, M L MARKS, D A BULL, and S E LITWIN

382 Diabetic Neuropathic Cachexia
A GODIL, D BERRIMAN, S KNAPIK, M NORMAN, F GODIL, and A F FIREK

TOPICS IN PRIMARY CARE MEDICINE

386 Approach to Patients With Hirsutism
R SAKIYAMA

EDITORIALS

392 What We See Most, We Understand Least
S K AGARWAL and H L JUDD

393 The Search for Viable Myocardium
R O BONOW

CORRESPONDENCE

397 Violence in America • Response • Do Premedical Students Fear Being Sued?

LESSONS FROM THE PRACTICE

399 Hypoglycemia in Bosnia
R HAMER

OTHER FEATURES

339 Subscription Information

341 Special Issues

342 Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming

400 Volume Index

407 In Memoriam

408 Classified Advertising

411 Business and Subscription Information

412 Western State Medical Associations' Meetings

Detailed Table of Contents: 336, 338, 340

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Please see brief summary of prescribing information for contraindications, warnings, precautions, adverse reactions, and dosage and administration on adjacent page.

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References: 1. Neu HC, Wilson APR, Grüneberg RN. Amoxycillin/clavulanic acid: a review of its efficacy in over 38,500 patients from 1979 to 1992. *J Chemother* 1993;5:67-93. **2.** *Clinical Efficacy Updates I-IV,* 1996, SmithKline Beecham Pharmaceuticals.

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BRIEF SUMMARY. FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT.
INDICATIONS AND USAGE: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below
Lower Respiratory Tract Infections caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Otitis Media* caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Sinusitis* caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Skin and Skin Structure Infections* caused by β-lactamase-producing strains of *Staphylococcus aureus, Escherichia coli*, and *Klebsiella* spp. *Urinary Tract Infections* caused by β-lactamase-producing strains of *E. coli, Klebsiella* spp. and *Enterobacter* spp. While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic. Because amoxicillin has greater *in vitro* activity against *Streptococcus pneumoniae* than does ampicillin or penicillin, the majority of *S. pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin and *Augmentin*. (See Microbiology subsection.)
Bacteriological studies to determine the causative organisms and their susceptibility to *Augmentin* should be performed together with any indicated surgical procedures. Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once results are known, adjust therapy, if appropriate.
CONTRAINDICATIONS: Patients with a history of allergic reactions to any penicillin, or patients with a history of *Augmentin*-associated cholestatic jaundice/hepatic dysfunction.
WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH *AUGMENTIN*, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.** Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic associated colitis." After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis. Use *Augmentin* cautiously in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with *Augmentin* use is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. (See CONTRAINDICATIONS and ADVERSE REACTIONS.)
PRECAUTIONS: **General**: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.
A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.
Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin. Co-administration of probenecid cannot be recommended. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.
Drug/Laboratory Test Interactions: Oral administration of *Augmentin* will result in high urine concentrations of amoxicillin. High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin and therefore *Augmentin*, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Tes-Tape®) be used.
Following administration of ampicillin to pregnant women a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone and estradiol has been noted. This effect may also occur with amoxicillin and therefore *Augmentin*.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. **Mutagenesis**: The mutagenic potential of *Augmentin* was investigated *in vitro* with an Ames test, a human lymphocyte cytogenetic assay, a yeast test and a mouse lymphoma forward mutation assay, and *in vivo* with mouse micronucleus tests and a dominant lethal test. All were negative apart from the *in vitro* mouse lymphoma assay where weak activity was found at very high, cytotoxic concentrations.
Impairment of Fertility: *Augmentin* at oral doses of up to 1200 mg/kg/day (5.7 times the maximum human dose, 1480 mg/m²/day, based on body surface area) was found to have no effect on fertility and reproductive performance in rats dosed with a 2:1 ratio formulation of amoxicillin/clavulanate.
Teratogenic effects: Pregnancy (Category B): Reproduction studies performed in pregnant rats and mice given *Augmentin* at oral dosages up to 1200 mg/kg/day, equivalent to 7200 and 4080 mg/m²/day, respectively (4.9 and 2.8 times the maximum human oral dose based on body surface area), revealed no evidence of harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.
Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.
Nursing Mothers: Ampicillin class antibiotics are excreted in the milk, therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.
ADVERSE REACTIONS: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were mild and transient, <3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.
The following adverse reactions have been reported for ampicillin class antibiotics:
Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis, mucocutaneous candidiasis and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.) Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome) and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis). These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin. (See WARNINGS.) A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. Interstitial nephritis and hematuria have been reported rarely. Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*. Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.
DOSAGE AND ADMINISTRATION
Since both the *Augmentin* 250 mg and 500 mg tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), 2 *Augmentin* 250 mg tablets are not equivalent to 1 *Augmentin* 500 mg tablet. Therefore, 2 *Augmentin* 250 mg tablets should *not* be substituted for 1 *Augmentin* 500 mg tablet.
Dosage:
Adults: The usual adult dose is 1 *Augmentin* 500 mg tablet every 12 hours or 1 *Augmentin* 250 mg tablet every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be 1 *Augmentin* 875 mg tablet every 12 hours or 1 *Augmentin* 500 mg tablet every 8 hours.
Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with a glomerular filtration rate of <30 mL/minute should not receive the 875 mg tablet. Patients with a glomerular filtration rate of 10 to 30 mL/minute should receive 500 mg or 250 mg every 12 hours, depending on the severity of the infection. Patients with a less than 10 mL/minute glomerular filtration rate should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection.
Hemodialysis patients should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection. They should receive an additional dose both during and at the end of dialysis.
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals. (See WARNINGS.)
Pediatric Patients: Pediatric patients weighing 40 kg or more should be dosed according to the adult recommendations.
Due to the different amoxicillin to clavulanic acid ratios in the *Augmentin* 250 mg tablet (250/125) versus the *Augmentin* 250 mg chewable tablet (250/62.5), the *Augmentin* 250 mg tablet should *not* be used until the pediatric patient weighs at least 40 kg or more.
Administration: *Augmentin* may be taken without regard to meals, however, absorption of clavulanate potassium is enhanced when *Augmentin* is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, *Augmentin* should be taken at the start of a meal.
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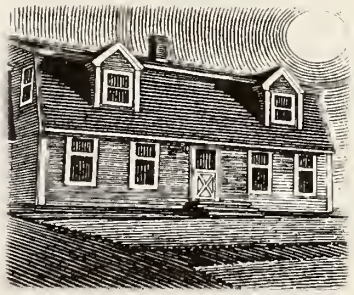

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VOLUME 165 • NUMBER 6 • DECEMBER 1996

CONTENTS

ARTICLES

349 **Onychomycosis—New Therapies for an Old Disease**

ADITYA K. GUPTA, MD; RICHARD K. SCHER, MD; PIET DE DONCKER, PhD; DANIEL N. SAUDER, MD; and NEIL H. SHEAR, MD

From the Division of Dermatology, Department of Medicine, and the Division of Clinical Pharmacology, Department of Pharmacology, Sunnybrook Health Science Center and the University of Toronto Faculty of Medicine, Toronto, Ontario; the Department of Dermatology, Columbia University College of Physicians and Surgeons, New York, New York; and the Janssen Research Foundation, Beerse, Belgium.

352 **Avoiding Medication Mixups—Identifiable Imprint Codes**

PRIYA VASUDEVAN, MB,BS; TERESA DEL GIANNI, PharmD, BCPS; and WILLIAM O. ROBERTSON, MD

From the Washington Poison Center, the Pharmacy Department, Children's Hospital and Medical Center, and the Department of Pediatrics, University of Washington School of Medicine, Seattle.

CONFERENCES AND REVIEWS

355 **Lung Transplantation—Part I. Indications and Operative Management**

DOUGLAS E. WOOD, MD, and GANESH RAGHU, MD

From the Section of General Thoracic Surgery, Lung Transplantation, and the Chest Clinic, University of Washington School of Medicine, Seattle.

364 **Myocardial Viability**

YOCHAI BIRNBAUM, MD, and ROBERT A. KLONER, MD, PhD

From the Heart Institute, Good Samaritan Hospital, and the University of Southern California, Los Angeles.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Obstetrics and Gynecology

Items of progress in nuclear medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

372 **Prematurity—Steroids for All**

ELLIOTT K. MAIN, MD

373 **Intracytoplasmic Sperm Injection**

ROBERT D. NACHTIGALL, MD

373 **Androgen Replacement in Postmenopausal Women**

HOMER G. CHIN, MD

374 **Adolescent Contraception**

ANITA L. NELSON, MD

376 **Managing Viral Exposure During Pregnancy**

JAMES D. GOLDBERG, MD

377 **Assisted Reproductive Technologies**

RICHARD J. PAULSON, MD

(Continued on Page 338)

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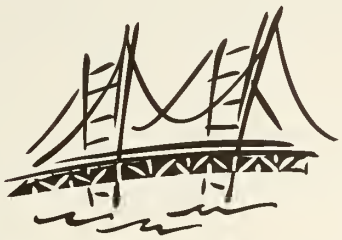

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Video-Assisted Pulmonary Metastasectomy—Port Site Metastasis

Spinal Brucellosis in a Southern California Resident

Epitomes, Editorials, Commentary, Lessons From The Practice

(Continued from Page 336)

ALERTS, NOTICES, AND CASE REPORTS

379 **Ruptured Sinus of Valsalva Aneurysm in a Patient With Autosomal Dominant Polycystic Kidney Disease**

ROBERT F. SPRUNG, MD; RENZO M. CATALDO, MD; MARTIN C. GREGORY, MD; MELINDA L. MARKS, MD; DAVID A. BULL, MD; and SHELDON E. LITWIN, MD

From the Divisions of Cardiology, General Internal Medicine and Nephrology, and Cardiothoracic Surgery, University of Utah Medical Center, and the Veterans Affairs Medical Center, Salt Lake City.

382 **Diabetic Neuropathic Cachexia**

ASLAM GODIL, MD; DIANE BERRIMAN, MD; STEVE KNAPIK, DO; MICHAEL NORMAN, DO; FOUZIA GODIL, MD; and ANTHONY F. FIREK, MD

From the Division of Gastroenterology and Nutrition, General Internal Medicine and Endocrinology, Jerry L. Pettis Veterans Affairs Medical Center and Loma Linda University and School of Medicine, Loma Linda; and Department of Internal Medicine, Desert Valley Medical Group, Victorville, California.

TOPICS IN PRIMARY CARE MEDICINE

386 **Approach to Patients With Hirsutism**

ROLAND SAKIYAMA, MD

From the Division of Family Medicine, University of California, Los Angeles, School of Medicine.

EDITORIALS

392 **What We See Most, We Understand Least**

SANJAY K. AGARWAL, MB,BS, and HOWARD L. JUDD, MD

From the Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, and the Department of Obstetrics and Gynecology, UCLA School of Medicine and Olive View/UCLA Mecial Center, Los Angeles, and Sylmar, California.

393 **The Search for Viable Myocardiam**

ROBERT O. BONOW, MD

From the Division of Cardiology, Northwestern University Medical School, Chicago, Illinois.

CORRESPONDENCE

397 **Violence in America**

DAVID C. STOLINSKY, MD

SUSAN B. SORENSON, PhD, and LAWRENCE D. CHU, MS, RESPOND

398 **Do Premedical Students Fear Being Sued?**

THOMAS F. HESTON, MD

LESSONS FROM THE PRACTICE

399 **Hypoglycemia in Bosnia**

ROD HAMER, MD

From the Student Health Services, University of California, Santa Barbara.

(Continued on Page 340)

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WJM1096

(Continued from Page 338)

OTHER FEATURES

337 Coming in the January Issue of WJM

339 WJM Subscription Information

341 WJM Special Issues

342 Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming

347 Classified CME Advertising

400 Volume Index

407 In Memoriam

408 Classified Advertising

411 Business and Subscription Information

412 Western State Medical Associations' Meetings

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

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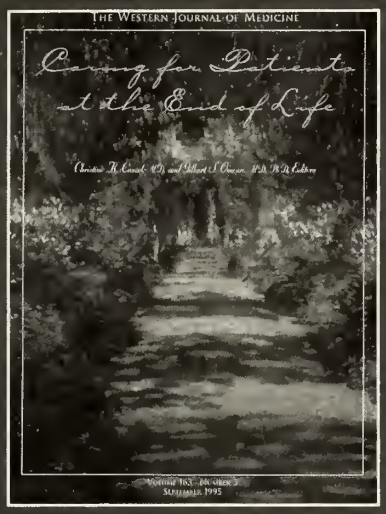

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February 6-8, 1997—**Epidemiology and Prevention of Infectious Diseases: Emerging Pathogengs in the US and Worldwide.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 14.5 hrs. $415–$470. Contact: UCSF.

February 20-27, March 6-13—**Epidemiology and Prevention of Vaccine-Preventable Diseases.** Thurs. CDC at Distance Learning Centers. Thurs. 3.5 hrs. Contact: California Distance Learning Health Network, Claudia Kratzenstein, (619) 594-3351.

ANESTHESIOLOGY

January 8-11—**Anesthesiology Update 1997.** UCSD at Hotel del Coronado, Coronado, Wed-Sat. 21 hrs. $375. Contact: UCSD.

January 31-February 2—**35th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Los Angeles at Sheraton Universal Hotel, Universal City. 15 hrs. $295. Contact: David J. Stewart, MB, Prog. Dir., Pediatric Anesthesiology Conf., Children's Hospital Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

CARDIOLOGY

January 24-26, 1997—**Clinical Nuclear Cardiology: Case Review With the Experts.** American College of Cardiology at Los Angeles. Fri-Sun. Contact: ACC, (800) 253-4636, ext 695.

March 13–15—**7th Annual Symposium on Coronary Stenting.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs–Sat. Contact: Laurel Steigerwald, Conference Coordinator, Dept. Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, 92037. (619) 554-8556.

March 15—**Heart Disease in Women—Where Are They Now?** American College of Cardiology at Anaheim. Contact: ACC, Extramural Programs, 9111 Old Georgetown Rd., Bethesda, MD, 20897-1448.

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January 17–19, 1997—**Practical Dermatology for the Primary Care Physician, San Diego.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Regency, La Jolla, San Diego. Method, AV, L, SB, W. $495. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

January 31–February 2—**Primary Care Dermatology.** UCSD at San Diego Hilton Beach and Tennis Resort. Fri-Sun. Contact: UCSD.

DRUG ADDICTION

April 17-20, 1997—**28th Annual Meeting of the American Society of Addiction Medicine.** American Society of Addiction Medicine at San Diego. Thurs-Sun. Contact: ASAM, Louisa Macpherson, Conference Coordinator, (910) 452-4920.

EMERGENCY MEDICINE

December 16-20—**Emergency Medicine Symposium II.** UCSD. Mon-Fri. 32 hrs. $495. Contact: UCSD.

February 17-21, 1997—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton Beach and Tennis Resort. 32 hrs. $495. Contact: UCSD.

March 2–7—**17th Annual Mammoth Mountain Emergency Medicine Ski Conference.** Mammoth Lakes, Calif. Sun-Fri. 18 hrs. $395 physicians, $275 residents and PAs, $225 nurses. Contact: Daniel Abbott, MD, Medical Conferences, Inc., PO Box 52-B, Newport Beach, Calif. 92662. 714-650-4156.

March 24–15—**Emergency Medicine Symposium II.** UCSD at San Diego. Mon-Fri. 32 hrs. $495. Contact: UCSD.

April 24–25—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Thurs-Fri. 16 hrs. $495. Contact: UCSD.

May 12–16—**Emergency Medicine Symposium I.** UCSD at La Jolla Marriott, San Diego. Mon–Fri. 32 hrs. $475. Contact: UCSD.

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January 20-22—**Opthalmology and ENT for the Primary Care Physician.** CMEA at Hyatt Regency, La Jolla. Mon-Wed. 20 hrs. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego, 92198. (800) 993-2632 or (619) 674-5200.

January 31-February 2—**Primary Care Dermatology.** UCSD at San Diego Hilton Beach and Tennis Resort. Fri-Sun. Contact: UCSD. (619) 534-3940.

January 31-February 1-2—**35th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital, Los Angeles, at Sheraton Universal Hotel, Universal City. 15 hrs. $295. Contact: David J. Stewart, MB, Program Director, Pediatric Anesthesiology Conference, Children's Hospital Los Angeles, PO Box 54700, Los Angeles, CA 90054. (213) 669-2262.

February 7-8—**15h Annual UC Davis Infectious Disease Conference.** UC Davis at Sacramento Hilton Inn. 10.5 hrs. $175. Fri.–Sun. Contact: UCD.

February 7-10—**CAFP 49th Annual Scientific Assembly.** CAFP at Hyatt Regency, San Francisco, Fri-Mon. $275-$385. Contact: Clark W. Franklin, CAFP, 114 Sansome St., Ste. 1305, San Francisco, CA 94104-3824. (415) 394-9121.

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February 16-21—**12th Annual Primary Care Medicine: Concepts and Controversies.** UCSF at Squaw Creek, CA 20 hrs. $625. Contact: UCSF.

February 17-20—**Clinical Hematology and Oncology: 1997.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Scripps, (619) 554-8556.

February 19-23—**The Practicing Physician's Approach to the Difficult Headache Patient.** Dannemiller Memorial Educational Foundation at Marriott's Las Palmas Resort and Country Club, Rancho Mirage. Wed-Sun. 22 hrs. $345. Contact: Meeting Coordinator, Diamond Headache Clinic Research and Educational Foundation, 467 West Deming Place, Chicago, IL, 60614. (312) 388-6363.

February 21—**Modern Approaches to Allergic Diseases for the Primary Care Physician.** UCSF at Moscone Center, San Francisco. Fri. 6.75 hrs. $125. Contact: UCSF.

February 28–March 2—**Office Gynecology and Women's Health for the Primary Care Physician.** CMEA at Hyatt Islandia, San Diego, Fri.-Sun. 20 hrs. $475. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego 92198. (800) 993-2632 or (619) 674-5200.

March 6-8—**Contraceptive Technology Conference.** Contemporary Forums at Fairmont Hotel, San Francisco. Thurs-Sat. 16 hrs. $425. Contact: Contemporary Forums, 11900 Silvergate Drive, Dept 265, Dublin, CA, 94568. (510) 828-7100.

March 7—**23rd Annual Diabetes Symposium.** UC Davis at Beverly Garland Hotel, Sacramento. Fri. $130. Contact: UCD.

March 20—**Diabetes Update.** UCSF at Holiday Inn, San Francisco. 7.5 hrs. $185. Contact: UCSF.

March 21-22—**Advances in Endocrinology and Metabolism.** UCSF at Holiday Inn, San Francisco. Fri-Sat. 13 hrs. $295. Contact: UCSF.

March 26-28—**Annual Review in Family Medicine.** UCSF at Stanford Court Hotel, San Francisco. Wed-Fri. 16 hrs. $375. Contact: Program Coordinator, Dept. Family and Community Medicine, 500 Parnassus Ave, MU-3E, San Francisco, CA 94143-0900. (415) 476-5250.

April 3-6—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** CMEA at Royal Sonesta Hotel, New Orleans, LA. Thurs-Sun. 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego 92198. (800) 993-2632.

April 9-13—**Annual Scientific Program and Postgraduate Course in Fertility.** Pacific Coast Fertility Society at Rennaissance Esmeralda Resort, Indian Wells. Wed-Sun. 19 hrs. Contact: Director of Medical Education or Susan Reddy Butler, Pacific Coast Fertility Society, PO Box 1656, La Mirada, CA, 90637-1656. (310) 947-7068.

April 14-15—**Born Too Soon: Multidisciplinary Strategies for Prevention of Preterm Birth.** Contemporary Forums at Marriott Hotel, Oakland. Mon-Tues. 13 hrs. $375. Contact: Contemporary Forums, 1900 Silvergate Dr., Dept. 280, Dublin, CA, 94568. (510) 828-7100, ext. 0.

April 17-20—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** CMEA at San Diego Hilton Beach and Tennis Resort. Thurs-Sun. 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego 92198. (800) 993-2632.

May 14–17—**Wound Management Workshop for Primary Care.** UCSD at La Jolla Marriott, San Diego. Wed–Sat. 15 hrs. $475. Contact: UCSD.

May 16–20—**Primary Care Essentials.** CMEA at Grand Hyatt on Union Square, San Francisco. Fri–Tues. 32 hrs. $750. Contact: Jacqueline Shiller, CMEA, PO Box 270469, San Diego, 92198 (800) 993-2632.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

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GERIATRICS

April 19, 1997—**Geriatrics Medicine Moves Into the 21st Century: Beyond the Basics.** UC Davis, Sacramento. Sat. 20 hrs. Contact: UCD.

May 3, 1997—**Geriatrics Medicine Moves Into the 21st Century: Beyond the Basics.** UC Davis, Sacramento. Sat. 20 hrs. Contact: UCD.

May 31, 1997—**Geriatrics Medicine Moves Into the 21st Century: Beyond the Basics.** UC Davis, Sacramento. Sat. 20 hrs. Contact: UCD.

INFECTIOUS DISEASE

February 6-8, 1997—**Epidemiology and Prevention of Infectious Diseases.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

INTERNAL MEDICINE

February 12-14, 1997—**Recent Adventures in Neurology.** UCSF at Hyatt Regency Hotel, San Francisco. Wed-Fri. 15 hrs. Contact: UCSF.

February 15-20—**22nd Annual Postgraduate Topics & Advances in Internal Medicine.** UCSD at Hyatt Regency, San Diego. Sat-Thurs. 52 hrs. $1365. Contact: UCSD.

February 17-20—**Clinical Hematology and Oncology: 1997.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Scripps, (619) 554-8556.

March 21-27—**Internal Medicine 1997.** CMEA at Hotel del Coronado, San Diego. Fri-Thurs. 45 hrs. $795. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

April 5—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Sat. 6 hrs. Contact: Laurel Steigerwald, Conference Coordinator, Dept. Academic Afairs, 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, 92037. (619) 554-8556.

NEPHROLOGY

February 6-8, 1997—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Hotel del Coronado, San Diego. Thurs-Sat. 17 hrs. $395. Contact: UCSD.

NEUROLOGY

January 17–19, 1997—**Advances in the Diagnosis and Clinical Practice in the Neurosciences.** San Diego Hilton Beach and Tennis Resort, San Diego. Fri.–Sun. 7 hrs. Contact: California Association of Neurological Surgeons, (916) 443-0236.

ONCOLOGY

February 17-20, 1997—**Clinical Hematology and Oncology: 1997.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Scripps, (619) 554-8556.

February 20-22, 1997—**Molecular Advances in Cancer Epidemiology and Prevention.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

OTOLARYNGOLOGY

January 4-8, 1997—**Temporal Bone Surgical Dissection Course.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, 2100 W Third St, Los Angeles 90057. (213) 483-4431, ext 7079.

February 1-5—**Temporal Bone Surgical Dissection Course.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs. $1,300. Contact: House Ear Institute, (213) 483-4431, ext 7079.

March 15-19—**1996-1997 Temporal Bone Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat-Wed. 48 hrs. $1300. Contact: Antonio de la Cruz, MD, Director of Educaiton, House Ear Institute, 2100 W Third St, Los Angeles, CA 90057. (213) 483-4431, ext 7079.

April 12-16—**1996-1997 Temporal Bone Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat-Wed. 48 hrs. $1300. Contact: Antonio de la Cruz, MD, Director of Educaiton, House Ear Institute, 2100 W Third St, Los Angeles, CA 90057. (213) 483-4431, ext 7079.

May 3–7—**1996-1997 Temporal Bone Survival Dissection Courses.** House Ear Institute at Los Angeles. Sat–Wed. 48 hrs. $1,300. Contact: The House Ear Institute, Antonio De la Cruz, MD, Director of Education, 2100 W. Third St., Los Angeles, 90057. (213) 483-4431.

PEDIATRICS

January 15-18, 1997—**San Diego Cerebral Palsy Symposium.** Children's Hospital at San Diego Marriott Mission Valley. Wed-Sat. 21.5 hrs, $450-$495. Contact: Continuing Medical Education, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

January 27-31— **San Diego Conference on Responding to Child Maltreatment.** Children's Hospital at Town and Country Hotel, San Diego. Mon-Fri. 30.5 hrs, $435. Contact: Registration Coordinator, Center for Child Protection, 3020 Children's Way (MC5016), San Diego 92123. (916) 495-4940.

January 31-February 2—**35th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Los Angeles at Sheraton Universal Hotel, Universal City. 15 hrs. $295. Contact: David J. Stewart, MB, Program Dir, Pediatric Anesthesiology Conf., Children's Hospital Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

February 1—**Update in Behavioral/Developmental Pediatrics.** UCSF at UCSF Campus. Sat. Contact: UCSF.

February 17–20—**Clinical Hematology and Oncology.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon–Thurs. 24 hrs. Contact: Laurel Steigerwald, Conference Coordinator, Dept. Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, 92037. (619) 554-8556.

February 17-19—**Pediatrics Update 1997.** CMEA at Hyatt Islandia, San Diego. Mon.–Wed. 20 hrs. $475. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 28-March 2—**Current Concepts in Pediatric Medicine—10th Anniversary.** Children's Hospital and Health Center at San Diego Hilton Beach and Tennis Resort. Fri-Sun. 16 hrs. $365. Contact: Children's Hospital, CME, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

March 21–27—**Pediatrics Update 1997.** CMEA at Buena Vista Palace at Walt Disney World Village, Orlando, FL. Mon.–Wed. 20 hrs. $475. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

April 4-5—**Pediatric Dermatology for the Practitioner.** Children's Hospital at Hyatt Islandia Mission Bay, San Diego. Fri-Sat. 12 hrs. $245. Contact: CME Office–5021, 3020 Children's Way, San Diego, CA. 92123. (619) 576-4072.

April 4–6—**Nelson Butters' West Coast Neuropsychology Conference: New Neuropsychological Tests for School-Aged Children.** UCSD at US Grant Hotel, San Diego. Fri–Sun. 15.5 hrs. $325. Contact: Cass Jones, Professional Conference Management, Inc. 7916 Convoy Court, San Diego, 92111. (619) 565-9921.

May 15–17—**30th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs–Sat. 15.5 hrs. $375. Contact: UCSF.

PLASTIC SURGERY

March 20–22, 1997—**9th Annual Symposium on Aesthetic Surgery.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 18 hrs. $950. Contact: UCSF.

PSYCHIATRY AND NEUROLOGY

February 12-14, 1997—**Recent Adventures in Neurology.** UCSF at Hyatt Regency Hotel, San Francisco. Wed.-Fri. 15 hrs. Contact: UCSF.

April 3-6—**Nelson Butler's West Coast Psychiatry Conference.** UCSD at US Grant Hotel, San Diego. Thurs-Sun. 15 hrs. $325. Contact: UCSD.

RADIOLOGY

January 26-February 2, 1997—**Multi Specialty Radiology Courses: Neuroradiology, Angiographic, Interventional, Chest, Ultrasound, and Bone.** UCSD at Hotel del Coronado, San Diego. Sun-Sun. Various hours. $975. Contact: Ryals & Associates, Inc, PO Box 1925 Roswell, GA. 30077-1925. (770) 641-9773.

March 29—**10th Annual Spring Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 6.25 hrs. $145. Contact: UCSD.

March 30-April 4—**17th Annual San Diego Residents Radiology Review.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 41 hrs. $695. Contact: UCSD.

SURGERY

January 4-8, 1997—**Temporal Bone Surgical Dissection Course.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs. $1,300. Contact: House Ear Institute, 2100 W Third St, Los Angeles 90057. (213) 483-4431, ext 7079.

GENERAL/MULTIDISCIPLINARY

December 12-14—**Diagnosis and Treatment of Back Pain—The Next Level.** St Mary's Hospital at Stanford Court Hotel, San Francisco. Thurs-Sat. Contact: Aubrey A. Swartz, MD, American Back Society, St Joseph's Professional Center, 2647 E 14th St, Ste 401, Oakland 94601. (510) 536-9929.

January 8, 1997—**Pre-ACLS Workshop.** AHA at San Leandro. Wed. 6 hrs. $50-$70. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro, CA 94577. (510) 632-6135.

January 17, 18, 19—**ACLS Renewal/Provider.** AHA at San Leandro. Fri-Sun. 6 hrs. $100. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro, CA 94577. (510) 632-6135.

January 22–25—**Medicine Meets VR—Global Healthcare Grid: Transformation of Medicine Through Communication.** UCSD at San Diego Marriott Hotel & Resort. Wed–Sat. Contact: Alligned Management Associates, (619) 749-2498.

February 1-2—**PALS Instructor.** AHA at San Leandro. Sat-Sun. 16 hrs. $170. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro, CA 94577. (510) 632-6135.

February 8-9—**ACLS Instructor.** AHA at San Leandro. Sat-Sun. 16 hrs. $195. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro, CA 94577. (510) 632-6135.

April 24-25—**New Frontiers in Alzheimer's Disease.** UCSD at San Diego Hilton. Thurs-Fri. 16 hrs. $210.

May 13—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at Scripps Clinic, La Jolla. Sat. 7 hrs. Contact: Laurel Steigerwald, Conference Coordinator, Dept. Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, 92037. (619) 554-8556.

HOME STUDY/SELF-ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

January 16–19, 1997—**Anxiety Disorders: Colorado Psychiatirc Association Annual Meeting.** Vail. Thurs–Sun. Contact: Laura Michaels, 759-6045.

February 16–21—**23rd Annual Vail Obstetrics & Gynecology Conference.** University of Colorado. Vail. Sun–Sun. Contact: Linda Woodstock, 372-9026.

February 23–26—**Team Approach to Pediatric Cardiac Disease.** The Children's Hospital. Vail Cascade Hotel and Club. Sun–Wed. Contact: Alice L. Kay, 861-6123.

March 1–7—**CRASH 97 Colorado Review of Anesthesia and Ski Holiday.** University of Colorado Dept. of Anesthesiology. Vail. Sat–Fri. Contact: Phyllis Tuller, 372-6901.

March 15–19—**Thoracic Transplantation 1997: An International Update.** Division of Cardiothoracic Surgery, University of Colorado. Marriott's Mountain Resort, Vail. Sat–Wed. Contact: U of Colo, 270-3065.

March 15–21—**Reconstructive Surgery of the Hip and Knee.** University of Colorado, Aspen. Sat–Fri. Contact: Joan Bauer (800) 882-9153.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

This listing of continuing medical education programs in Idaho is compiled by the Ada County Medical Society. To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930.

Brochures, course information, and registration forms are available from the contact person or organization.

February 14–16, 1997—**ACMS 28th Annual Medical Winter Clinics.** Shore Lodge Inn, McCall, Idaho. Fri-Mon. 9 hrs. Contact: Judy Barningham (208) 336-2930 or Marie Chester (208) 381-2135.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

January 11-12, 1997—**15th Albuquerque Family Practice Seminar.** Albuquerque Hilton. Sat.-Sun. Contact: Ann Woodrow, Albuquerque Academy of Family Physicians, 2309 Renard SE, #208, Albuquerque, NM 87106. (505) 243-4560.

February 28-March 1—**25th Annual New Mexico Thoracic Society Lung Disease Symposium.** Taos. Fri-Sat. Contact: Billie Dytzel, 216 Truman NE, Albuquerque 87108. (505) 265-0732; (800) 221-LUNG. FAX (505) 260-1739.

April 6–9—**9th Annual Southwest Regional Substance Abuse Conference. Prevention and Treatment—Turning Obstacles Into Opportunities.** Al-

buquerque Marriott Hotel. Contact: SWRSAC, 1479 Morning Glory Rd, NE, Albuquerque, NM 87122. (505) 856-1717, FAX (505) 856-1490.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

February 5-9—**3rd Annual Brigham & Women's Utah Therapeutic GI Endoscopy Course 1996: Problems and Solutions.** Park City. Contact: UUSM.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS:	Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

December 12–14—**Annual Meeting: Washington State Chapter American College of Physicians**. Seattle. Thur.-Sat. Contact: U/W CME (206) 543-1050.

December 12–14—**The 12th Annual Infectious Disease Conference**. Seattle. Thur.-Sat. Contact: PNCEI (360) 653-4543.

December 13—**Alternative Medicine 1996**. Bellevue. Fri. Contact: Group Health Cooperative of Puget Sound (206) 326-3441.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

OTHER CME OPPORTUNITIES

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

AMERICAN CANCER SOCIETY. February 20–22, 1997—**National Conference on State of the Art in Cancer Genetics: Societal and Clinical Implications of DNA Testing**. Hyatt Reunion, Dallas, Texas. 19 hrs. $325. Thurs.–Sat. Contact: Iris Goodson, American Cancer Society, 1599 Clifton Rd., NE, Atlanta, GA 30329-4251. (404) 329-7604, FAX (404) 329-5713.

AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE. May 9–16, 1997—**56th Annual American Occupational Health Conference**. Orange County Convention Center, Orlando, Fla. Fri.–Fri. Contact: ACOEM, 55 W. Seegers Rd., Arlington Heights, Ill 60005. (847) 228-6850, FAX (847) 228-1856.

THE CENTER FOR BIO-MEDICAL COMMUNICATION, INC. March 7–9—**Management of the HIV-Infected Patient—A Practical Approach for the Primary Care Practitioner**. Crowne Plaza Manhattan, New York City, NY. Fri.–Sun. Contact: Center for Bio-Medical Communication, Inc. (201) 385-8080, FAX (201) 385-5650.

CREIGHTON UNIVERSITY SCHOOL OF MEDICINE. July 9–11, 1997—**14th Annual Scientific Session of the American Association of Clinical Anatomists**. Honolulu. Wed–Fri. Contact: Sally C. O'Neill, PhD, Associate Dean, Creighton University CME Division, 601 North 30th St., Suite 2130, Omaha, NE 68131. (800) 548-CMED or (402) 280-1830.

CREIGHTON UNIVERSITY SCHOOL OF MEDICINE, July 12, 1997—

CONTINUING MEDICAL EDUCATION

Clinical Anatomy of the Basic Physical Examination. Honolulu. Sat. Contact: Sally C. O'Neill, PhD, Associate Dean, Creighton University CME Division, 601 North 30th St., Suite 2130, Omaha, NE 68131. (800) 548-CMED or (402) 280-1830.

INSTITUTE FOR JEWISH MEDICAL ETHICS. February 14–17 1997—**8th Annual International Conference on Jewish Medical Ethics**. San Francisco. Fri–Mon. 27 units CME credit. Jointly sponsored by the Institute for Jewish Medical Ethics of San Francisco and Stanford University School of Medicine. Contact: IJME, (800) 258-4427.

NATIONAL MANAGED HEALTH CARE CONGRESS. January 28–31, 1997—**6th Annual West Managed Health Care Congress**. Palm Springs, Calif. Contact: NMHCC. (617) 505-8000, FAX (617) 270-600.

PHYSICIANS FOR A VIOLENCE-FREE SOCIETY. February 7–8—**4th Annual Conference: "Alcohol: Fuel for Family Violence?"** Hyatt at Fisherman's Wharf, San Francisco, Calif. Contact: JoAn Dwyer, PO Box 35528, Dallas, TX 75235-0528. (214) 590-8807, FAX (214) 590-4079.

UNIVERSITY OF NEBRASKA. February 14, 1997—**Cardiovascular Research Symposium**. Omaha. Fri. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. March 2–7—**17th Annual Keystone Conference: Review of Head and Neck Medicine for the Primary Care Physician**. Omaha. Sun–Fri. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. March 10–21—**Family Practice Review: Skills for the 21st Century**. Omaha. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. March 20–22—**National Association of Medical Direction of Respiratory Care**. Omaha. Thu–Sat. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE. March 21–22, 1997—**Integrated Care of the Thoracic Surgery Patient—A Seminar for Allied Health Professionals**. St. Louis, Mo. Fri.–Sat. Contact: Office of Continuing Medical Education, Washington University School of Medicine, Campus Box 8063, 660 South Euclid Ave., St. Louis, Mo 63110-1093. (800) 325-9862, FAX (314) 362-1087.

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE. April 4–5—**Clinical Pulmonary Update**. St. Louis, Mo. Fri.–Sat. Contact: Office of Continuing Medical Education, Washington University School of Medicine, Campus Box 8063, 660 South Euclid Ave., St. Louis, Mo 63110-1093. (800) 325-9862, FAX (314) 362-1087.

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE. April 10–12—**Refresher Course & Update in General Surgery**. The Ritz-Carlton Hotel, St. Louis, Mo. Thu.–Sat. Contact: Office of Continuing Medical Education, Washington University School of Medicine, Campus Box 8063, 660 South Euclid Ave., St. Louis, Mo 63110-1093. (800) 325-9862, FAX (314) 362-1087.

NOTICE

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Articles

Onychomycosis
New Therapies for an Old Disease

ADITYA K. GUPTA, MD, *Toronto, Ontario*; RICHARD K. SCHER, MD, *New York, New York*;
PIET DE DONCKER, PhD, *Beerse, Belgium*; *and* DANIEL N. SAUDER, MD, *and* NEIL H. SHEAR, MD, *Toronto, Ontario*

The newer generation of antifungal agents such as itraconazole and terbinafine are more effective than the older therapies, griseofulvin and ketoconazole, in the treatment of dermatophyte pedal onychomycosis. Itraconazole can be administered as continuous dosing, 200 mg per day for 3 months, or in the form of pulse therapy, 200 mg twice a day for 1 week per month for 3 consecutive months. Terbinafine is given as continuous dosing, 250 mg per day for 3 months.

(Gupta AK, Scher RK, De Doncker P, Sauder DN, Shear NH: Onychomycosis—New therapies for an old disease. West J Med 1996; 165:349–351)

Until recently, the only two important oral medical therapies for pedal onychomycosis were griseofulvin and ketoconazole, with low cure and high relapse rates.[1–5] This often led to frustration and disappointment in both physicians and patients. Itraconazole was approved for use in the treatment of dermatophyte onychomycosis in the United States in 1995, and onychomycosis has been a labeled indication for terbinafine use in Canada since May 1993 and in the United States since May 1996. The newer antifungal agents are likely to supersede griseofulvin and ketoconazole for the treatment of pedal onychomycosis.

We have reviewed the salient features of these two drugs using the case histories of a husband and wife with onychomycosis as illustrative examples. One spouse's condition cleared with itraconazole therapy and the other's with terbinafine.

Report of Cases

Case 1

The patient, a 71-year-old man, presented with a 20-year history of onychomycosis. Several years ago, he was treated with griseofulvin, but the disease recurred a year later. The patient had also tried applying ketoconazole cream to the affected toenails, again without response. There was distal and lateral subungual onychomycosis with 40% nail-plate disease of the right big toe and 60% of the left big toe—distance from the proximal nail fold to the onychomycotic border was 8 mm and 4 mm for the right and left big toenails, respectively. Material collected from the toenails was positive for potassium hydroxide (KOH), and the culture grew *Trichophyton rubrum*.

Case 2

The patient, the wife of patient 1, aged 68 years, had had onychomycosis of 16 years' duration. About 14 years ago, she, too, had been placed on griseofulvin therapy. This had produced some clinical response, but she discontinued therapy because of gastrointestinal side effects. She later tried topical ketoconazole cream, again without response. There was distal and lateral subungual onychomycosis with 60% nail-plate disease of the right big toe and 40% of the left big toe—distance from the proximal nail fold to the onychomycotic border was 4 mm and 9 mm for the right and left big toenails, respectively. In this patient, the KOH test was also positive, and the culture grew *T rubrum*.

Both the husband and wife presented with onychomycosis of several years' duration that had not responded to griseofulvin therapy or several topical treatments. The couple was keen to have normal-looking toenails because they were embarrassed about wearing footwear in the summer where their toenails would be exposed to the public. Patient 1 was placed on a regimen of terbinafine given as continuous dosing, 250 mg per day for 12 weeks. Patient 2 was started on itraconazole intermittent pulse therapy given as 200 mg twice a day for one week each month for a total of three months. While on itraconazole therapy, she was taking nifedipine and atenolol for hypertension. Ankle edema developed that may have been the result of an interaction between itraconazole and nifedipine. This drug interaction is the subject of a separate report.[6] There was complete cure in both patients when seen in follow-up 12 months after discontinuing therapy.

From the Division of Dermatology, Department of Medicine, and the Division of Clinical Pharmacology, Department of Pharmacology, Sunnybrook Health Science Center and the University of Toronto Faculty of Medicine, Toronto, Ontario (Drs Gupta, Sauder, and Shear); the Department of Dermatology, Columbia University College of Physicians and Surgeons, New York, New York (Dr Scher); and the Janssen Research Foundation, Beerse, Belgium (Dr De Doncker).

ABBREVIATIONS USED IN TEXT

KOH = potassium hydroxide
SE = standard error of the mean

Discussion

For the past 35 years or so, griseofulvin therapy has been the mainstay for the management of onychomycosis.[1,2] Before that, pedal onychomycosis was essentially incurable. Following therapy with griseofulvin, the cure rate of onychomycosis of the toenails was poor (0% to 17%),[3–5] even after several months of therapy. Also, relapse rates with griseofulvin use were relatively high, 33% to 40%.[4,7]

Ketoconazole was the next important oral antifungal agent that became available for the treatment of onychomycosis in the early 1980s. Cure rates for toenail onychomycosis were again generally poor in most series: 11%,[3] 19%,[8] 21%,[4] and 65%.[9] Within three to four years of the introduction of ketoconazole, the drug was found to be associated with both transient asymptomatic elevations of serum aminotransferase or alkaline phosphatase levels or symptomatic hepatic reactions.[10–13] Symptoms were reported as early as 2 days after starting therapy and as long as 365 days, with a mean of approximately two months.[13] The reaction is thought to be idiosyncratic in nature and unrelated to the duration of therapy, daily dosage, or cumulative total dose.[12–14] The incidence of hepatotoxicity, primarily of the hepatocellular type, is about 1 per 10,000.[15] The hepatic injury has usually, but not always, been reversible.[15]

Terbinafine, an allylamine antifungal agent, is effective in the treatment of dermatophyte onychomycosis.[16,17] The recommended dosage is 250 mg per day given continuously for 12 weeks.[18] In published studies, the complete cure of toenail onychomycosis caused by dermatophytes has been reported in 41% to 71% patients.[18–22]—meta-analytic average ± standard error of the mean (SE), 95% confidence interval: 62 ± 6%, 50% to 74%. With itraconazole, the currently advocated regimen for the treatment of pedal onychomycosis is an intermittent pulse of 200 mg twice a day for one week, given once a month for three or four cycles.[23] Complete cure of toenail onychomycosis caused by dermatophytes occurred in 64% and 72% patients receiving the three-pulse and four-pulse regimen, respectively.[23] The itraconazole regimen that has been currently approved for use in the United States is 200 mg per day given as continuous dosing for three months. A complete cure with this regimen has been reported to occur in 36% to 61% of patients[20,21,24–26]—meta-analytic average ± SE, 95% confidence interval: 50 ± 9%, 31% to 68%. It is likely that one-week pulse courses of itraconazole will become the preferred dosing strategy for onychomycosis.

Both itraconazole and terbinafine are much more effective than griseofulvin. We ought to caution patients that the use of the newer antifungal agents does not result in a complete cure every time. Also, longer durations of itraconazole or terbinafine therapy should be considered with lateral nail-plate or matrix disease[27] or when the area of diseased nail plate exceeds 75% of the nail bed and involves the nail matrix. Reports suggest that itraconazole may be more effective than terbinafine in the treatment of nondermatophyte molds and yeasts.[28–30]* Furthermore, the relapse rate with itraconazole and terbinafine use approximately a year after stopping therapy is 9% to 21%[7,25,31,32] compared with 33% to 40% with the use of griseofulvin.[4,7] With a longer follow-up period, the relapse rates are likely to be higher. In some patients, there may be a genetic susceptibility to the development of *T rubrum* onychomycosis and tinea pedis.[33] Strategies to prevent reinfection of onychomycosis must include the prevention of tinea pedis because this condition may facilitate the development of onychomycosis.

The pharmacokinetic and pharmacodynamic properties of terbinafine and itraconazole enable these drugs to be extremely effective even when used for short courses of therapy. The growing nail plate receives a contribution from both the matrix of the lunula and, to a lesser extent, the nail bed.[34,35] Both terbinafine and itraconazole have been detected in peripheral fingernail clippings within a week of the initiation of therapy.[36,37] These and other studies suggest that both terbinafine and itraconazole move rapidly into the nail plate by diffusing from the nail bed, in addition to being taken up into the newly formed nail at the nail matrix.[38–40] In contrast, griseofulvin probably reaches the nail plate through the nail matrix.[40] Furthermore, both terbinafine and itraconazole persist in nails for several months following the discontinuation of oral therapy.[23,24,41] In contrast, griseofulvin may not persist in the nail plate for more than two weeks after therapy is discontinued.[42]

Whenever possible, the clinical diagnosis of onychomycosis should be confirmed with a positive KOH test and culture. The choice of antifungal agent may, in part, be dictated by the cultured organism(s). Concomitant drug therapy is another factor that needs to be considered when deciding which antifungal agent should be used, as highlighted by the case of patient 2. There are currently no firm guidelines regarding laboratory monitoring during the treatment of onychomycosis with the new-generation antifungal agents.[43] Whenever possible, pretherapy blood work should be done. Experience with the use of these drugs will help establish guidelines for monitoring during therapy.

Reported adverse effects with itraconazole use include gastrointestinal disturbances, reversible elevations in liver enzyme levels, headache, menstrual disorder, rash, and dizziness.[31,34] Itraconazole may interact with several drugs, and in particular, coadministration with terfenadine, astemizole, cisapride, oral midazolam, and oral triazolam is contraindicated. With terbinafine use, reported

*P. De Doncker, G. Ginter, J. Decroix, et al: "Intermittent Pulse Therapy With Itraconazole for the Treatment of Nondermatophyte Onychomycosis": theme of poster at the American Academy of Dermatology meeting, February 1995, New Orleans, Louisiana.

adverse effects include headache, gastrointestinal disturbances, reversible elevation in liver enzyme levels, rash, and visual and taste disturbance.[32] Terbinafine has fewer drug interactions compared with itraconazole, with the more important ones being with cimetidine and rifampin.

Other promising therapies for the management of onychomycosis include fluconazole.[45,46] Topical agents may be of some benefit as an adjunct to oral treatment or as monotherapy in cases of mild to moderate onychomycosis, with less than about 50% distal nail-plate disease in the absence of matrix involvement. Examples include 5% amorolfine, 8% ciclopirox nail lacquer, and 28% tioconazole nail solution.[47–53]

Conclusion

The modern management of onychomycosis finally offers patients with this condition a chance of cure, even those with severe nail dystrophy. The new generation of antifungals has pharmacokinetic properties that enable treatment periods to be shortened, while providing high efficacy rates.

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Articles

Avoiding Medication Mixups
Identifiable Imprint Codes

PRIYA VASUDEVAN, MB,BS; TERESA DEL GIANNI, PharmD, BCPS; *and*
WILLIAM O. ROBERTSON, MD, *Seattle, Washington*

This study was done to determine if current imprinting of solid medication forms permits health care professionals to identify the manufacturers involved so as to be able to activate the hierarchic identification system mandated by the Food and Drug Administration. We tested 15 representatives of 6 groups of health professionals for their ability to identify the manufacturer after having examined 30 solid-dosage forms drawn from a pseudo-random sample of stock hospital formulary products. The correct identification of the manufacturer was the sole criterion. Of the 2,700 opportunities, the manufacturer was able to be identified for only 43%. Nurses and medical students had a 35% success rate, pharmacists and poison center specialists a 55% success rate, and residents and attending physicians a 40% rate. None approached 95% accuracy. Currently employed imprints fail in their objective to permit health care professionals—or the general public—to rapidly identify prescription drugs. The manufacturers' logotypes need to be modified if this identification system is to be implemented. We propose a simple voluntary collaborative effort by the pharmaceutical industry to solve the problem.

(Vasudevan P, Del Gianni T, Robertson WO: Avoiding medication mixups—Identifiable imprint codes. West J Med 1996; 165:352–354)

Confronted by a burgeoning number of new pharmaceutical products in the late 1950s, the American Medical Association commissioned J. J. Hefferren, PhD, to develop a feasible mechanism for health care professionals to identify unknown tablets and capsules more rapidly and accurately. His solution involved constructing a ten-digit code for each solid-dosage medication form based on its unique physical characteristics.[1] Although theoretically sound, the resultant technique failed miserably in practice—consuming more than 15 minutes to reach an unacceptable 35% accuracy rate.[2] Variations on this theme proved no more effective. Unknown solid-dosage forms remained unknown until Eli Lilly Pharmaceutical Company developed and promulgated its "Identicode" system in 1967. This involved imprinting Lilly's name (logotype) plus a unique three-digit alphanumeric code on each of its solid-dosage products. When tested in practice, that technique achieved a 98% accuracy rate in less than 15 seconds—a dramatic improvement over all previous options.[3]

Over the decade of the 1970s, more than 90% of major prescription drug manufacturers adopted the imprinting technique—and over-the-counter drug manufacturers began to imprint their products as well. In 1980 the state of Washington was the first to adopt and implement legislation mandating the imprinting of all prescription solid-dosage forms—both trade name and generic products. Over the subsequent decade, more than 20 other states followed Washington's example so that virtually all such prescription medications were theoretically identifiable first by the manufacturer's name and then as to the individual product.

In 1991 the Washington legislature extended its mandate to apply to all nonprescription (over-the-counter) drugs as well. The legislature, however, agreed to postpone implementing that edict until after the Non-Prescription Drug Manufacturers Association had an opportunity to petition the Food and Drug Administration (FDA) to adopt a nationwide standard for imprinting of all solid-dosage forms so as to avoid having individual states mandate possibly conflicting imprinting requirements. After almost two years of discussion and debate on the matter, the FDA did adopt such a regulation in September 1993, choosing to retain the current "hierarchic" coding system. In general, this entails first identifying the manufacturer (or distributor) and then the manufacturer's unique product.[4]

The FDA's final regulations went into effect on September 19, 1995; all health care professionals, their patients, and the general public have access to precise

From the Washington Poison Center (Drs Vasudevan and Robertson), the Pharmacy Department, Children's Hospital and Medical Center (Dr Del Gianni), and the Department of Pediatrics (Dr Robertson), University of Washington School of Medicine, Seattle.

Reprint requests to William O. Robertson, MD, Medical Director, Washington Poison Center, 155 NE 100th St, Ste 400, Seattle, WA 98125-8012.

labeling information on each individual solid medication product. Such information has already proved effective in identifying "unknown medications" involved in accidental or purposeful overdoses, in avoiding dispensing errors, or in minimizing patient confusion between and among tablets or capsules after they have been taken home and removed from their original container to be stored in a pocket or purse.[5]

We postulate that the use of the technique might contribute to solving the widespread problem of "drug errors" in hospitals where, based on eight years of data from New York State, some 860 accidental deaths are projected to occur annually in our nation's hospitals.[6] For the technique to be effective, however, it first must enable users to identify accurately the manufacturer (or the distributor) from the name, logotype, symbol, or trademark imprinted on the tablet or capsule. To date, this step has presented problems.

In April 1992, Smolinski and Robertson published a report casting substantial doubt on the ability of even specially trained health professionals to achieve such identifications.[7] Attendees at the annual meeting of toxicologists could barely achieve an accuracy rate of 10% in deciphering admittedly selected logotypes. Unfortunately, no corrective actions followed. We decided to quantify the degree of accuracy able to be achieved by representatives of various groups of health care professionals when challenged to interpret the name of the manufacturer of a sample of 30 imprinted solid-dosage forms of common prescription drugs.

Methods

Two of us, an experienced pharmacist (T.D.G.) and a physician (P.V.), reviewed various solid-dosage forms on the formulary in a hospital approved by the Joint Commission on Accreditation of Healthcare Organizations, seeking a representative sample (n = 30) of the products with reference to their size, shape, color, and imprinting features. Five examples of each product—some trade name products and others generic products—were collected from single stock bottles (Figure 1). Each was placed in a separate plastic envelope and the entire sample was sequenced in a pseudo-randomized manner and subsequently attached to single white sheets of paper for inserting into three-ring binders. The physician proceeded to conduct all assessments to ensure uniformity of instructions, observations, and recordings. We had sought 15 volunteers from each of several readily accessible groups of health care professionals—pharmacists, poison information specialists, attending physicians, resident physicians, medical students, and registered nurses—hypothesizing that pharmacists and poison information specialists (all of whom were acquainted with and had actually used Micromedix Inc's computerized "Identidex" based on imprinting features) would be considerably more accurate than medical students or nurses in recognizing the manufacturers' names or symbols, with resident physicians and attending physicians falling somewhere in between the other two groups in their respective success rates. With careful attention to lighting in the room, decreasing possible distractions, and providing a hand-held magnifying glass, we allowed each volunteer as long as 15 seconds to examine each unknown medication so as to identify the specific manufacturer. Anything other than the correct answer was scored as an error.

Results

Virtually every individual health care professional approached agreed to participate; many volunteered the information that the study seemed long overdue because of specific problems they had already noted in attempting to identify unknown medicines. Thus, we rapidly secured 15 volunteers for each of the six groups: none took more than a total of ten minutes to complete the entire exercise, including the reading of specific directions before the experiment itself.

As seen in Table 1, the 30 manufacturers' names have

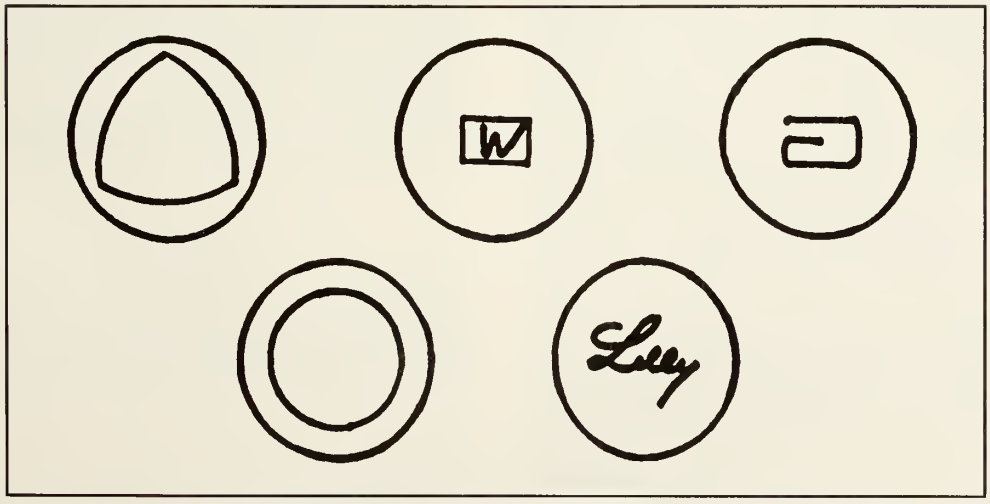

Figure 1.—Shown are 5 examples of logotypes from solid-dosage medication forms from which to identify the manufacturer.

TABLE 1.—*Descending Order of Correctly Identified Manufacturers (90 choices each)*

Name of Manufacturer	*Identified Correctly, No. (%)*	
Eli Lilly	90	(100)
Geigy Pharmaceutical	89	(99)
Glaxo Pharmaceutical	89	(99)
Wallace Laboratories	88	(98)
McNeil Pharmaceutical	88	(98)
Rugby	87	(97)
Roche Laboratories	86	(96)
DuPont Pharma	85	(94)
Biocraft Laboratories*	84	(93)
Adria Laboratories	76	(84)
Merck-Sharp-Dohme	50	(56)
A.H. Robins	42	(47)
Parke-Davis	41	(46)
Abbott Laboratories	37	(41)
Lederle Laboratories	31	(34)
Sandoz Pharmaceuticals	24	(27)
Danbury Pharmaceutical	16	(18)
Geneva Pharmaceutical	14	(16)
Sanofi Winthrop Pharmaceuticals	14	(16)
Sidmark Laboratories	5	(6)
Schering Corporation	4	(4)
Schiapparelli Searle	4	(4)
Roxane Laboratories	3	(3)
Purepac	2	(2)
Purdue Frederick Company	2	(2)
Biocraft Laboratories*	2	(2)
Johnson & Johnson Merck	0	(0)
Braintree Laboratories	0	(0)
Chase Laboratories	0	(0)
Winthrop Pharmaceuticals	0	(0)

*Manufacturer employed two different logotypes after corporate reorganization.

TABLE 2.—*Comparison of Accuracy Rates Among Health Professional Groups**

Group	*Correct Choice, No. (%)*	
Pharmacists	246	(55)
Poison center specialists	244	(54)
Physicians, attending	185	(41)†
Residents	168	(37)‡
Medical students	156	(35)
Nursing personnel	154	(34)
Totals	1,153	(43)

*Each group had 450 choices, for a total number of 2,700.
†The first 2 groups differed significantly from the third group, $P < .001$.
‡The fourth group differed significantly from the last 2 groups, $P < .05$.

been sequenced by the decreasing order of their recognizability from the imprint. For the first 7, 95% or more of the manufacturers' imprints were correctly identified; all had the name of the company spelled out on the capsule or tablet itself. In contrast, for the bottom 11, no such clarity of interpretation was to be found through the imprint symbol; of the 990 selection opportunities for those 11 products, only 20 (2.2%) were able to be accurately identified as to the specific manufacturer. Overall, among the sample of tablets and capsules selected for the study, two thirds presented problems to our subjects as they sought to identify the manufacturer involved. Hence, the step of interpreting the manufacturer's symbol or logotype presented a substantial barrier to precise identification of the specific products in question.

When the six participating groups were compared for their respective performances, there were some statistically significant differences between and among several of them as noted in Table 2. Such differences would seem of no practical importance because no group came close to achieving a "passing grade" (70%) or our sought-for accuracy rate of greater than 95%, which would seem a reasonable goal for any effective identification system.

Discussion

Although current technology is clearly able to make unit identification of unknown tablets and capsules virtually instantaneously available, its day-to-day use prohibits any meaningful reliance on this identification system. Whereas some pharmaceutical companies have chosen to optimize the potential of the identification system, others appear to have lagged considerably in achieving any such success. If a company's name is too lengthy to imprint, a derivative three-digit unique abbreviation of its name would certainly suffice—assuming that the Pharmaceutical Research and Manufacturers of America or a comparable group, the United States Pharmacopeial Convention, Incorporated, would serve voluntarily to develop a coordinated system for assigning "authorized abbreviations."

It is our premise that neither a health professional nor a member of the general public should have to rely on a specially trained third party to decipher imprints on solid-dosage forms. Were names or three-digit abbreviations to replace manufacturers' other logotypes or symbols, unit dose identification would immediately become feasible. Moreover, we are confident that were manufacturers to modify their tablet and capsule labeling by ensuring that the imprint was interpretable, they would improve their current image with the public. Thus, we strongly urge a voluntary effort to achieve this objective. Although conceivably bar coding or some other technology may eventually supersede imprinting, clear communication to consumers must remain the paramount objective to be achieved.

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Conferences and Reviews

Lung Transplantation
Part I. Indications and Operative Management

DOUGLAS E. WOOD, MD, *and* GANESH RAGHU, MD, *Seattle, Washington*

In the past 8 years, lung transplantation has become a standard therapy for benign end-stage pulmonary disease. Rapid advances have occurred involving indications and operative management that have allowed pulmonary transplantation to be a viable option for an increasingly diverse patient population. In part I, we review the current indications and operative techniques, and in part II we will cover the postoperative management and results.

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Lung transplantation has rapidly become an accepted therapy for end-stage respiratory disease. Although the first reported human lung transplantation was performed by Hardy in 1963, it was not until 28 years later that the Toronto, Ontario, lung transplantation group performed the first successful single lung transplantation for pulmonary fibrosis. A small clinical experience was accumulated, primarily in Toronto, from 1983 to 1988. Since 1988 increasing experience with lung transplantation has led to the emergence of 90 lung transplantation centers in the United States and 124 centers worldwide reporting to the International Lung Transplant Registry in 1996.[1,2] During this time, there has been a progressive improvement in recipient selection criteria and preoperative management, donor management and organ preservation, operative techniques, immunosuppressive management, and surveillance strategies for postoperative infection and rejection. These clinical improvements have resulted in one-year survival rates as high as 90% for single-lung transplantation and 85% for bilateral lung transplantation. The clinical indications for lung transplantation have increased simultaneously, with 2,113 patients in the United States on waiting lists for pulmonary transplantation in July 1996. In 1995, however, 342 patients on lung transplant waiting lists died while waiting for a suitable lung donor.[2]

An inadequate supply of suitable lung donors remains the principal limitation in lung transplantation today. Many strategies for increasing the number of donor organs have been used: aggressive public education programs, and the use of marginal donors and living-related lung donors. Unfortunately, these strategies are likely to remain limited until there is clinical success with cadaveric or xenotransplantation. Bronchiolitis obliterans is the leading cause of late morbidity and mortality in lung transplant recipients, affecting from 20% to 50% of long-term survivors. Bronchiolitis obliterans is most likely the pathologic result of long-term rejection, but its pathogenesis and treatment are currently poorly understood. Improvements in the understanding and management of bronchiolitis obliterans are essential to the continued success and development of lung transplantation so that lung transplant recipients may achieve a measure of success similar to that of other solid-organ recipients.

Historical Perspective

Initial experimental lung transplantation in animals occurred in the 1940s and 1950s. Neptune and co-workers reported the earliest experimental results of lung transplantation in the United States, in which they substituted a left atrial anastomosis for separate venous anastomoses.[3] Initial investigators documented a loss of graft function due to rejection five to seven days after transplantation.[4] Hardy and colleages were able to prolong graft survival in a dog single-lung-transplant model with the use of methotrexate, azathioprine, and hydrocortisone.[5]

The first human lung transplantation was performed at the University of Mississippi Medical Center, Jackson, in 1963.[6] The recipient, a 58-year-old man with squamous cell carcinoma of the left main-stem bronchus, had underlying emphysema with inadequate pulmonary reserve to tolerate a pneumonectomy. The donor lung was harvested after death from a patient who sustained a cardiac arrest due to a myocardial infarction. The recipient died 18 days later of complications of renal failure. Azathioprine, steroids, and thymic irradiation were used for immunosuppression. At autopsy, vascular integrity and normal pulmonary parenchyma with

From the Section of General Thoracic Surgery (Dr Wood), Lung Transplantation (Drs Wood and Raghu), and the Chest Clinic (Dr Raghu), University of Washington School of Medicine, Seattle.

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Reprint requests to Douglas E. Wood, MD, Division of Cardiothoracic Surgery, Box 356310, University of Washington School of Medicine, Seattle, WA 98195.

ABBREVIATIONS USED IN TEXT

COPD = chronic obstructive pulmonary disease
FEV_1 = forced expiratory volume in 1 second
Fio_2 = fraction of inspired oxygen
PEEP = positive end-expiratory pressure

no signs of pulmonary rejection were found. From 1963 to 1983, more than 40 pulmonary transplantations were done.[7] The longest survivor lived ten months, including an eight-month hospital stay after having received a right single-lung transplant for end-stage silicosis.[8] About 50% of the patients died within the first week of transplantation due to primary organ failure from poor preservation or rejection. Patients surviving more than a week after transplantation died of infection, rejection, or complications of the bronchial anastomosis, and 80% of recipients surviving more than seven days had major complications due to the bronchial anastomosis. Cooper and coinvestigators from Toronto evaluted the factors affecting bronchial anastomotic healing.[4] They concluded that high doses of steroids given postoperatively adversely affected bronchial healing, that cyclosporine used as an alternative to prednisone increased bronchial healing, and that donor ischemia was a major etiologic factor in the development of bronchial anastomotic complications. Unlike with all other solid-organ transplantations, the systemic artery circulation (bronchial) was not routinely reestablished during transplantation, with a donor bronchus relatively ischemic and dependent on retrograde collaterals between the pulmonary and bronchial circulations. Bronchial omentopexy was developed in a canine model, and bronchial collateralization occurred within four days with excellent healing of the bronchial anastomosis.[9,10]

A review of the world experience with lung transplantation by the Toronto group in the early 1980s also underscored the terminal condition of most previous recipients, who were often ventilator-dependent, infected, and in multiorgan system failure.[4] Obviously, successful outcomes could be enhanced by selecting patients before the onset of multisystem failure; yet, clinical experience needed to be limited to patients with a short life expectancy. Patients with end-stage idiopathic pulmonary fibrosis appeared to be the ideal candidates, both because of their short life expectancy and because the underlying pulmonary fibrosis and increased pulmonary vascular resistance would favor both ventilation and perfusion to a newly transplanted lung.

It was in this setting that the Toronto group performed the first successful human lung transplantation in 1983.[11] The patient, a 58-year-old man with end-stage pulmonary fibrosis, was discharged after six weeks and survived for 6½ years. In patients with obstructive disease, concern about a possible ventilation-perfusion mismatch and native lung herniation with mediastinal shift led to the initial application of bilateral lung transplantation.[12] The initial approach of en bloc double-lung transplantation was technically difficult, requiring anastomoses of the trachea, main pulmonary artery, and donor left atrium on full cardiopulmonary bypass. This procedure was initially used for patients with chronic obstructive pulmonary disease (COPD) and septic lung disease such as cystic fibrosis and bronchiectasis, but was accompanied by a high morbidity and mortality from bleeding complications and fatal airway complications. Other centers simultaneously used heart-lung transplantation as an alternative to double-lung transplantation. Although this procedure was technically easier and had a lower rate of airway complications, bleeding complications remained high in patients with septic lung disease, with a mortality of 25% to 30%.[4] Furthermore, heart-lung transplantations limited the number of thoracic organs that were available and subjected the recipient to both the early and late complications associated with heart transplantation. Only part of this problem was solved by the development of "domino" transplantation, with a heart-lung transplant recipient donating their otherwise healthy heart to a secondary heart transplant recipient.

Both en bloc double-lung transplantation and heart-lung transplantation were essentially eliminated by the development of sequential bilateral lung transplantation and evolving experience with single-lung transplantation.[13] Sequential bilateral lung transplantations by a bilateral thoracosternotomy made it possible to remove and replace each lung sequentially, usually avoiding the need for cardiopulmonary bypass altogether. This was technically easier than the en bloc double-lung transplantation with fewer bleeding complications and fewer complications of the bronchial anastomosis and has become the procedure of choice for double-lung transplantation.

Despite the early concerns regarding single-lung transplantation for emphysema, a series of successful single-lung transplantations was reported for patients with COPD.[14] Since that report, COPD has become the single most common indication for lung transplantation, though this may soon change with the introduction of and increasing experience with lung-volume-reduction surgery. Both single- and double-lung transplantations have now been used successfully for pulmonary vascular disease. Even patients with substantial right ventricular failure due to primary pulmonary hypertension have had good results following single-lung transplantation with subsequent cardiac recovery.[15] These results have allowed the application of single-lung transplantation with the repair of an intracardiac defect in patients with Eisenmenger's complex as well. These combined experiences have virtually eliminated the indications for heart-lung transplantation in most transplantation centers. The relative merits of single- versus double-lung transplantation for patients with pulmonary vascular disease remain controversial, with each technique being applied in a variety of centers.

With the reproducible results obtained in several centers and the development of various suitable indications, lung transplantation has matured past its developmental stage and has moved into the stage of improving long-term results. It is no longer considered "experimental." Limited donor supply and a poor ability to selectively

manipulate and target the immune response to an organ transplant remain the major limitations affecting lung transplantation and other solid-organ transplantations.

Indications

General Selection Criteria

Patients with severe, disabling, and benign pulmonary diseases that are refractory to currently available medical and surgical therapies are candidates for possible pulmonary transplantation. Because lung transplantation is still evolving, the indications and contraindications are being constantly modified. Although most transplantation centers follow generally accepted criteria, individual centers have their own guidelines based on experience. Transplantation is considered a viable treatment of last resort in selected patients because it does not yet have reliable long-term results. It is reserved for patients with a short life expectancy, and attempts are made to select patients with a one- to two-year life expectancy. Because of transplantation waiting lists and previous experience with severely ill, hospitalized patients in respiratory failure, attempts are made to select, evaluate, and enlist patients for transplantation before the terminal phase of their illness. Patients should have no other major systemic illness or malignant neoplasm that would compromise long-term results. Patients undergoing single-lung transplantation are generally younger than 65 years, and patients undergoing bilateral lung transplantation are generally younger than 60. Their nutritional status should be adequate, and they should generally be able to walk or undergo rehabilitative measures. Patients should have previously demonstrated compliance with medical regimens and not have contraindications to immunosuppression. A psychosocial evaluation is done on all possible recipients to ensure a stable and supportive outpatient environment and a psychologically stable patient with no recent history of alcohol or drug abuse. Cigarette smokers must totally abstain from cigarette smoking for four to six months before being considered for a lung transplantation evaluation.

Contraindications for lung transplantation include the presence of a multisystem disease that would limit the expected benefits from pulmonary transplantation. This includes especially patients with substantial renal or hepatic insufficiency. Patients are not accepted who are positive for the human immunodeficiency virus or have active sites of extrapulmonary infection. Notable osteopenia and osteoporosis are considered absolute contraindications in most transplantation centers. Pulmonary infection or colonization with *Aspergillus* species or panresistant organisms is generally considered a contraindication for lung transplantation. Patients should preferably be taking less than 20 mg per day of prednisone and be within 20% to 25% of their ideal body weight because of postoperative complications that occur in malnourished or obese patients. Finally, if patients are from an area not served by a transplantation center, they must be able to move to the region of a center while awaiting transplantation and through the early postoperative period. Pulmonary diseases appropriate for lung transplantation are listed in Table 1, and specific indications for transplantation in each disease are dealt with in the subsequent sections. Table 2 lists the standard pretransplantation evaluation performed at the University of Washington School of Medicine, Seattle.

Obstructive Lung Disease

Obstructive lung disease comprises primarily acquired smoking-related emphysema and α_1-antitrypsin deficiency. Emphysema now constitutes the most frequent single indication for lung transplantation today. In the subset of patients with emphysema, it has been particularly difficult to select the appropriate criteria for transplantation. This is because of a wide variation in survival data for patients with end-stage emphysema, particularly with the development of oxygen therapy for hypoxemia. Large multicenter trials have shown that patients with a forced expiratory volume in one second (FEV_1) of less than 30% and age younger than 65 years have a three-year survival rate of 50% to 70%.[16] A two-year survival rate of less than 50% in patients with COPD was associated with a Pa_{O_2} of less than 53 mm of mercury, an FEV_1 of less than 0.35 liters, or a mean pulmonary artery pressure of greater than 30 mm of mercury with the patients breathing room air.[17,18] More subjective criteria relate to patients' clinical course, with a rapidly progressive downhill course and frequent hospital admissions for exacerbations providing further indications for considering transplantation. In general, patients who are considered for transplantation are severely disabled, have an FEV_1 of less than 20% of predicted, usually have hypoxemia, hypercarbia, or both, and frequently a secondary pulmonary hypertension has developed. The indications for transplantation in patients with obstructive lung disease are rapidly changing, however, with the development of lung-volume-

TABLE 1.—*Indications for Lung Transplantation*

Single-Lung Transplant	*Bilateral Lung Transplant*	*Heart-Lung Transplant*
Emphysema	Cystic fibrosis	Eisenmenger's syndrome with complex cardiac defect
α_1-Antitrypsin deficiency	Bronchiectasis	Pulmonary hypertension with severe right-sided heart failure
Idiopathic pulmonary fibrosis	Emphysema	
Interstitial lung disease	α_1-Antitrypsin deficiency	
Primary pulmonary hypertension	Primary pulmonary hypertension	
Eisenmenger's syndrome	Eisenmenger's syndrome	

reduction surgery for end-stage emphysema. Patients with an FEV_1 of between 15% and 35% of predicted, pronounced hyperinflation documented by a total lung capacity of more than 120% of predicted, or a residual volume of more than 160% of predicted, without substantial pulmonary hypertension (mean pulmonary artery pressure < 35 mm of mercury), may be appropriate candidates for lung-volume-reduction surgery. Long-term results of lung reduction are not yet available, but this procedure avoids the complications of immunosuppression and rejection in appropriately selected patients. This treatment can delay or even prevent the need for transplantation in these patients and has the secondary benefit of allowing the scarce resource of donor lungs to be distributed among patients who do not have a similar medical or surgical alternative to transplantation.

Restrictive Lung Disease

Restrictive lung diseases are characterized by a decreased total lung capacity and vital capacity with a proportional decrease in expiratory flow rates. The most common pathologic disorder in this category in patients undergoing lung transplantation is idiopathic pulmonary fibrosis. Because of the restrictive pulmonary effects coupled with secondary pulmonary hypertension, patients with this disorder were selected as the ideal candidates for the initial successful attempts with single-lung transplantation. Furthermore, these patients commonly have a rapidly progressive downhill course. There is a large group of patients with interstitial lung diseases who also may be candidates for transplantation (Table 3).

Survival in patients with idiopathic pulmonary fibrosis varies widely, with some patients following a rapidly progressive course and dying within a few months of diagnosis and others living as long as 20 years.[19] The mean survival of these patients is four years, and one of the most important determinants is patients' response to corticosteroids, with a positive response producing a 43% five-year survival rate versus a 20% five-year survival rate in those unresponsive to steroid therapy.[20] The survival of patients with interstitial lung disease averages five years after the appearance of the first clinical signs, although this is a heterogenous group of diseases.[21] In general, being female, younger, and having a positive response to treatment result in a better prognosis.[22] The timing of referral for transplantation remains ill-defined because of the widely varying clinical courses that idiopathic pulmonary fibrosis and the interstitial lung diseases may follow. Patients showing signs of a downhill course despite medical therapy, with a vital capacity and total lung capacity of less than 50% of predicted, with resting hypoxemia (<60 mm of mercury) or resting hypercapnia (>46 mm of mercury), and the development of secondary pulmonary hypertension should be considered for a transplantation evaluation and listing.[21] Because of the commonly fulminant downhill course in patients with idiopathic pulmonary fibrosis, these patients are allocated an additional 90 days of waiting time credit beyond their initial listing date by the United Network of Organ Sharing to offset their relatively rapid course compared with other patients listed for pulmonary transplantation.

TABLE 2.—*Evaluation for Lung Transplantation*

Pulmonary medicine evaluation
Thoracic surgery evaluation
Hematology and coagulation panel
Chemistry panel—liver function and nutrition panel
Viral serologic tests—hepatitis B, hepatitis C, cytomegalovirus, HIV
Pulmonary function tests
Arterial blood gas measurements
Chest x-ray film and chest computed tomography (CT)
Screening sinus CT
Duplex examination of deep venous system
Duplex examination of carotid arteries and arterial system (selected patients)
Quantitative ventilation-perfusion scan
Bone densitometry for appropriate patients (postmenopausal women, corticosteroid use)
Echocardiogram
Right heart catheterization
Left heart catheterization—age >50 years or other indications
Rehabilitation medicine consultation
Psychosocial evaluation
Nutrition evaluation
Social work evaluation
Financial evaluation
Consultations
Rehabilation medicine
Physical therapy
Cardiology (selected patients)
Other disciplines or consultations (ad hoc, based on clinical needs)

HIV = human immunodeficiency virus

TABLE 3.—*Interstitial Lung Disease Indications for Lung Transplantation*

Sarcoidosis
Collagen vascular disorders
Lymphangioleiomyomatosis
Eosinophilic granuloma
Occupational lung disease
Chemotherapy- or radiation therapy-induced
Bronchiolitis obliterans organizing pneumonia
Others

Septic Lung Disease

Severe bilateral bronchiectasis is the final common pathway of the disease processes leading to a consideration of lung transplantation for septic lung disease. Cystic fibrosis is by far the most common cause of bronchiectasis in western society and the most common indication for pulmonary transplantation in the septic lung diseases. Other causes of bronchiectasis are childhood or adult pneumonia, tuberculosis, aspiration, and the ciliary dyskinesia syndrome. It is important to establish the cause of bronchiectasis preoperatively because it may affect the indications for transplantation as well as the postoperative management. By definition, bronchiectasis that is

severe enough to warrant transplantation is bilateral because unilateral or lobar disease can usually be treated medically or by surgical resection. The septic lung diseases are, therefore, the only absolute indication for bilateral rather than single-lung transplantation.

Respiratory failure is still the primary cause of death in patients with cystic fibrosis, which is the most common genetic disease in whites. The average life expectancy of patients with cystic fibrosis is still only into the mid-20s, although this is markedly improved with modern medical therapy.[23] In addition to the general recipient criteria already described, clear predictors of two-year survival have been described for patients with cystic fibrosis.[24] Patients with an FEV_1 of less than 30% of predicted, a Pa_{O_2} of less than 55 mm of mercury, or a Pa_{CO_2} of greater than 50 mm of mercury have a two-year mortality of greater than 50%. These objective data, combined with deteriorating respiratory failure, a severely impaired quality of life, and recurrent hospital admissions, provide the fairly clear-cut indications for pulmonary transplantation in patients with cystic fibrosis. In general, these criteria are also used for patients with bronchiectasis due to causes other than cystic fibrosis, but this is a much more heterogeneous group of patients with a less well-defined natural history.

Specific considerations for patients undergoing transplantation for septic lung disease are nutritional state, sinus and pulmonary colonization with resistant organisms, and possibly dense pleural adhesions. Aggressive attempts should be made to maximize nutrition in these frequently debilitated patients before listing them for transplantation. Infection or colonization with resistant organisms such as *Pseudomonas (Berkholderia) cepacia* is an absolute contraindication for transplantation at some centers, but the procedure is still considered at other centers if the organisms are sensitive to an appropriate antibiotic. *Aspergillus* species colonization is also a relative contraindication to transplantation in these patients. Patients with severe bronchiectasis will usually have a large number of dense pleural adhesions due to the chronic infective nature of their underlying illness. This is sometimes exacerbated by previous thoracic operations or treatments of pneumothoraces. These problems increase the technical challenges to the surgical team, but are not considered contraindications for transplantation.

Pulmonary Vascular Disease

Primary pulmonary hypertension is the most common pulmonary vascular disease in patients undergoing evaluation for lung transplantation. Eisenmenger's syndrome with secondary pulmonary hypertension due to a congenital cardiac defect is also a common indication. Patients with pulmonary veno-occlusive disease and specific cases of pulmonary hypertension due to thromboembolic disease may also be appropriate to consider for transplantation. Secondary pulmonary hypertension may develop in patients with restrictive, obstructive, and septic lung diseases (discussed earlier).

The estimated life expectancy of a patient with primary pulmonary hypertension is 2.8 years from the time of diagnostic catheterization.[25] Of these patients, however, 34% are alive at five years, and there is a subset of patients who respond well to high doses of calcium channel blockers with prolonged survival.[26] Still, 26% of these patients may have sudden death, and as many as half of them may die of a rapidly progressive course. The mean survival of patients with a mean pulmonary artery pressure of greater than 85 mm of mercury is 10 months. The mean survival of patients with a cardiac index of less than 2 is 17 months.[25] These objective criteria, combined with having New York Heart Association class III or IV disease and not being responsive to the use of pulmonary vasodilators, constitute the indications in pulmonary vascular disease for pulmonary transplantation. Common indications for considering lung transplantation in patients with pulmonary hypertension include a mean pulmonary artery pressure of greater than 60 mm of mercury, a cardiac index of less than 2, New York Heart Association class III or IV disease, or unresponsiveness to pulmonary vasodilators.

Nearly all patients with substantial primary pulmonary hypertension or Eisenmenger's syndrome will have a degree of right-sided heart failure. It is also apparent, however, that patients recover most of their right ventricular function when pulmonary vascular resistance is diminished by lung transplantation.[15] There appears to be no current index of right ventricular function that is useful as a criterion for rejecting patients for lung transplantation except for the secondary manifestations of right ventricular failure such as ascites, malnutrition, and liver failure. Although some favor heart-lung transplantation in patients with severe right ventricular dysfunction, there is no evidence that this improves the short- or long-term results in these patients. Similarly, patients with Eisenmenger's syndrome who have a correctable intracardiac defect such as an atrial or ventricular septal defect are best treated by single- or bilateral lung transplantation with a simultaneous cardiac correction. This leaves only patients with Eisenmenger's complex and incorrectable cardiac defects and those with left ventricular failure and pulmonary parenchymal or vascular disease as candidates for heart-lung transplantation.

Less common indications for lung transplantation are pulmonary veno-occlusive disease with similar hemodynamic indications as in patients with primary pulmonary hypertension. It is extremely important to exclude chronic pulmonary embolism as a factor in pulmonary hypertension in prospective transplant recipients. Some patients with chronic pulmonary emboli and peripheral disease not amenable to other surgical approaches may be treated by lung transplantation if they have severe pulmonary hypertension, right-sided heart failure, and correction of the underlying disease that led to chronic pulmonary emboli.

Donor Selection and Management

A paucity of suitable pulmonary donors is the most important limitation in the progress of pulmonary trans-

plantation today. There are an estimated 59 possible organ donors per million population per year,[27] translating to a potential of more than 15,000 donors in the United States annually. This verifies the approximation that only 10% to 20% of possible organ donors are used.[28] The failure of medical personnel to request organ donation and the denial of consent by relatives account for a large portion of lost donations.[28] Unfortunately, the subset of organ donors with lungs suitable for transplantation is even smaller and is estimated to be about 25% of heart donors.[29] Many organ donors are trauma victims and have suffered considerable chest trauma along with their closed-head injury, with pulmonary laceration or contusion preventing lung use. These patients with trauma or catastrophic neurologic events may also have aspirated at the time of injury, increasing the chance of a pulmonary infection precluding organ harvest. By definition, these patients are intubated, with colonization of the airway predisposing to pneumonia as well. The longer a patient is comatose and ventilated, the higher the risk for pulmonary infection, which prevents pulmonary organ use. A patient on mechanical ventilation for more than seven days seldom has lungs suitable for harvesting. Finally, pulmonary edema may result from either a neurogenic cause or aggressive fluid and blood product resuscitation in a trauma patient. This is often reversible with careful donor management, but may also be progressive and severe enough to preclude organ use. Massive trauma and blood transfusions may also lead to the adult respiratory distress syndrome in a possible donor and is a contraindication to lung harvest.

Donor Selection

The standard criteria for a suitable lung donor are listed in Table 4 and include age younger than 55 years, a clear chest roentgenogram, a Pa_{O_2} of greater than 300 mm of mercury on a fraction of inspired oxygen (Fi_{O_2}) of 1.0, and 5 cm of water of positive end-expiratory pressure (PEEP) without notable thoracic trauma, infection, or a smoking history.[30] Because of the progressive shortage of donors, many of these previously rigid criteria have been challenged and relaxed with the use of an increased number of "marginal" lung donors. Donors who are older than 55 years, have a substantial smoking history, have an abnormal chest x-ray film with unilateral or minor pulmonary contusion or edema, and have inadequate oxygenation due to unilateral disease have been considered "acceptable."[31] An aggressive approach to lung harvesting in cases of unilateral pulmonary disease has been successful.[32] In these cases, unilateral ventilation and cross-clamping of the pulmonary artery on the side of the disease have resulted in acceptable oxygenation and the ability to use the single lung that shows good gas exchange. With further experience, relaxation of the criteria for suitable lung donors may continue although with a possible detrimental effect on recipient results. This must be weighed against the problems of donor shortage and patient deaths while waiting for a transplant.

TABLE 4.—Lung Donor Criteria

Age < 55 years
Clear chest x-ray film
Pa_{O_2} > 300 mm of mercury (Fi_{O_2} of 1.0 and PEEP at 5 cm of water)
No purulent secretions or aspiration on bronchoscopy
No serious thoracic trauma
No previous thoracic operation
Smoking < 20 pack-years

Fi_{O_2} = fraction of inspired oxygen, PEEP = positive end-expiratory pressure

When suitable donors are identified, they must then be matched to appropriate recipients. ABO compatibility is a necessity, and prospective cross-matching is preferable if time and proximity permit. Cross-matching is mandatory for recipients with panel of reactive antibodies of 4% or more. Size matching is important because an overly large lung may interfere with venous return or develop atelectasis, and an undersized lung may produce pleural space problems or an inadequate pulmonary vascular surface area. An appropriate lung for transplantation approximates the ideal total lung capacity for the recipient.[33] Because total lung capacity is a function of height, age, and sex, the height of the recipient is the most important single indicator for donor size. Multiple measurements of chest circumference and x-ray film dimensions have been used, but none appear as accurate or as reliable as donor and recipient height matching. Recipients receiving bilateral lung transplants require much closer size matching than those undergoing single-lung transplantation. Oversizing of recipients of bilateral lung transplants will result in cardiac compression and poor venous return. For bilateral lung transplantation, we prefer the donor height to be within 7 to 10 cm of that of the recipient. Single-lung transplants have more flexibility owing to the ability of the mediastinum to shift. In patients undergoing single-lung transplantation for pulmonary fibrosis or pulmonary hypertension, we attempt to select donors within 10 cm of the recipients in height. Recipients with obstructive lung disease have hyperexpanded chests. If such a patient is undergoing a single-lung transplantation, it is preferable to place an oversized lung in the transplanted side to avoid pronounced hyperinflation of the native lung with mediastinal shift toward the transplant. In these cases, we prefer a donor who is 10 to 20 cm taller than the anticipated recipient. Unfortunately, this may create a problem for a large patient with COPD who may have difficulty matching with an even larger lung donor for single-lung transplantation. This may require the reconsideration of bilateral lung transplantation using a donor of equal or smaller size for these patients. Occasionally oversized lungs can be used with a downsizing maneuver such as middle lobectomy, lingulectomy, or bilateral wedge resections. When possible, however, we prefer to size donors and recipients appropriately without the need for pulmonary resection.

Donor Management

Organ donations usually result from multiple trauma, penetrating head injuries, or an intracranial hemorrhage.

Cardiac and pulmonary dysfunction often accompanies the head injury and may result in vasomotor instability and alterations in systemic vascular resistance and body temperature. Normothermia and hemodynamic stability should be maintained throughout resuscitative efforts and after the declaration of brain death. Before the introduction of lung transplantation, large fluid volumes were frequently used to maintain systemic pressure and kidney, liver, and cardiac function, even in the face of a low systemic vascular resistance. This may result in fluid overloading of the potential lung donor, however, with pulmonary edema compromising gas exchange, and may result in the lungs being lost for possible transplantation. A central venous pressure of 5 to 10 mm of mercury is generally sufficient to provide an adequate cardiac index, and systemic hypotension due to a low vascular resistance should be treated with low doses of α-sympathomimetic agents.

Brain death is accompanied by diabetes insipidus in 50% to 70% of organ donors.[34] A urine output of 1 to 2 liters per hour is not uncommon and can lead to electrolyte disturbances and hypovolemia. This is currently treated with desmopressin acetate, usually administered as a continuous infusion titrated to maintain a urine output of 100 to 200 ml per hour.

Aggressive measures to prevent secondary pneumonia in an intubated comatose patient are essential for the successful maintenance of the possible lung graft. Brain-injured patients may be initially treated with low tidal volumes and no PEEP, but once the criteria for brain death are met, ventilator management with adequate tidal volumes (10 to 15 ml per kg) and PEEPs of 5 cm water are important to maximize oxygenation, minimize the FiO_2, and minimize atelectasis. Meticulous pulmonary toilet should be maintained, both before and after the declaration of brain death, using sterile endotracheal suctioning techniques, frequent position changes, and chest physiotherapy.

Overall, success in obtaining suitable lung grafts is dependent on attention to detail from the moment of the initial injury. This requires educating neurosurgical and trauma teams caring for the patients before brain death and close cooperation between the abdominal and thoracic transplantation teams managing a patient once brain death and consent for donation have occurred.

Operative Technique

Donor Procurement

A number of techniques with minor variations have been described for thoracic organ procurement. We will describe the standard harvesting technique used at the University of Washington School of Medicine for heart transplantation, single-lung transplantation, double-lung transplantation, and any combination of these procedures. Commonly a single donor will provide thoracic organs for three recipients, with a donor procedure and three recipient procedures occurring simultaneously. The only modifications of this technique would be for harvesting of the heart-lung block for heart-lung transplantation, and these techniques have been described elsewhere.[35,36]

The technique for lung procurement done at the University of Washington is similar to that described by the Washington University (St Louis, Missouri) group.[30] A median sternotomy is performed, and the pleural spaces and the pericardium opened widely for physical examination of the heart and lungs to exclude evidence of trauma. The aorta, superior vena cava, and inferior vena cava are each encircled intrapericardially. When the abdominal transplantation team is ready for cross-clamping, cardioplegia and pulmonoplegia catheters are placed in the ascending aorta and the main pulmonary artery, respectively. Prostaglandin E_1 is administered directly into the pulmonary artery, followed by immediate aortic cross-clamping and the initiation of cardioplegia. Pulmonoplegia is initiated by instilling a modified Euro-Collins solution by gravity drainage, maintaining a perfusion pressure of 20 to 30 mm of mercury. Both pleural spaces and the pericardium are filled with ice slush for topical cooling, and the anesthesiologist maintains gentle hand ventilation to adequately distribute the pulmonary perfusate. We then prefer to remove the heart first, preserving a 5- to 8-mm cuff of left atrium on each pair of pulmonary veins. The lungs are removed as a double-lung block that can then be divided into a right and left lung block. The lungs are transported in an inflated condition in iced slush.

Single-Lung Transplantation

A standard posterolateral thoracotomy provides excellent access for single-lung transplantation. Most patients will tolerate single-lung ventilation in the absence of substantial pulmonary hypertension, allowing dissection of the hilar structures. If a patient tolerates single-lung ventilation without notable hypoxemia, hypercarbia, hemodynamic instability, or elevation of pulmonary artery pressures above a mean of 40 mm of mercury, then most will not require cardiopulmonary bypass. It is prudent, however, to test-clamp the pulmonary artery to ensure that the patient maintains stable hemodynamics. Moderate pulmonary hypertension may be responsive to the administration of pulmonary vasodilators. Marginal patients with refractory pulmonary hypertension greater than a mean of 40 mm of mercury or with profound hypotension, hypoxemia, or worsening hypercarbia warrant being placed on cardiopulmonary bypass. We prefer to err on the side of electively establishing cardiopulmonary bypass rather than to risk hemodynamic collapse and the need for emergency bypass during implantation.

A recipient pneumonectomy is performed when the donor lung becomes available. The main-stem bronchus is divided just proximal to the right upper lobe branch, and it is critical to not devascularize any portion of the recipient bronchus. The donor lung is prepared by completing dissection of the pulmonary artery and pulmonary venous cuffs. The donor bronchus is divided two rings, or about 1 cm, proximal to the upper lobe origin, and to avoid devascularization, no further peribronchial

dissection is performed.

The bronchial anastomosis is performed first with 6 to 7 mm of intussusception, producing an overlapping bronchial anastomosis. Peribronchial tissue is then used to cover the bronchial anastomosis to separate it from the subsequent pulmonary arterial anastomosis. The atrial wall between the two pulmonary veins is divided intrapericardially to create a single large left atrial orifice for the venous anastomosis, which can be done either before or after the arterial anastomosis. The recipient and donor pulmonary arteries are then examined for length and diameter. An anastomosis can be done proximal or distal to the initial recipient branch points to assist in size matching. Care must be taken to prevent an overly long pulmonary artery that may subsequently become kinked when the lung inflates.

The restoration of pulmonary blood flow and ventilation usually results in a prompt drop in pulmonary vascular pressures and rapid improvement in oxygenation. Routine bronchoscopy ensures the adequacy of the bronchial anastomosis before the procedure is completed. Attention to detail avoids most technical complications, probably the most common of which is bronchial anastomotic stricture or dehiscence. Careful anastomotic technique and the avoidance of excessive dissection will prevent most bronchial complications. Vascular complications are rare and avoidable—most commonly related to excessive length of the pulmonary artery or to narrowing of the anastomosis by "purse-stringing" of the anastomotic suture.

Bilateral Lung Transplantation

Candidates for bilateral lung transplantation are placed in the supine position for a bilateral thoracosternotomy (clamshell) incision. Patients with septic lung disease may have extensive adhesions that require tedious dissection in which meticulous hemostasis is extremely important. Using sequential single-lung ventilation, each pulmonary hilum is dissected as previously described for single-lung transplantation. Preoperative quantitative ventilation-perfusion scintigraphy combined with intraoperative observation will determine which side to use for the initial transplantation. Sequential test-clamping of the right and left pulmonary artery during respective single-lung ventilations is again done to determine the possible need for cardiopulmonary bypass. In patients in whom cardiopulmonary bypass is used, bilateral pneumonectomy can be done when the donor lungs become available. This may be especially useful in patients with septic lung disease in whom the removal of all infected pulmonary tissue before transplantation is optimal. In patients without pulmonary hypertension, we aggressively attempt to avoid cardiopulmonary bypass and its subsequent complications. When the donor lungs become available, a single-lung transplantation is done as previously described. After several minutes of reperfusion and ventilation on the newly transplanted lung, ventilation of the contralateral native lung can be ceased and pulmonary artery test-clamping again done. A contralateral pneumonectomy and transplantation procedure is performed, precluding the need for cardiopulmonary bypass. With the complete cardiac output being directed through a newly transplanted lung, pulmonary edema and elevated pulmonary artery pressures may develop, requiring the institution of cardiopulmonary bypass during the contralateral lung implantation. This is particularly the case if there has been an ischemic time of longer than four hours.

We discuss the postoperative management and the cumulative results of lung transplantation in part II of this review.

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Myocardial Viability

YOCHAI BIRNBAUM, MD, *and* ROBERT A. KLONER, MD, PhD, *Los Angeles, California*

Left ventricular function is a major predictor of outcome in patients with coronary artery disease. Acute ischemia, postischemic dysfunction (stunning), myocardial hibernation, or a combination of these 3 are among the reversible forms of myocardial dysfunction. In myocardial stunning, dysfunction occurs despite normal myocardial perfusion, and function recovers spontaneously over time. In acute ischemia and hibernation, there is regional hypoperfusion. Function improves only after revascularization. Evidence of myocardial viability usually relies on the demonstration of uptake of various metabolic tracers, such as thallium (thallous chloride Tl 201) or fludeoxyglucose F 18, by dysfunctional myocardium or by the demonstration of contractile reserve in a dysfunctional region. This can be shown as an augmentation of function during the infusion of various sympathomimetic agents. The response of ventricular segments to increasing doses of dobutamine may indicate the underlying mechanism of dysfunction. Stunned segments that have normal perfusion show dose-dependent augmentation of function. If perfusion is reduced as in hibernating myocardium, however, a biphasic response usually occurs: function improves at low doses of dobutamine, whereas higher doses may induce ischemia and, hence, dysfunction. But in patients with severely impaired perfusion, even low doses may cause ischemia. Myocardial regions with subendocardial infarction or diffuse scarring may also have augmented contractility during catecholamine infusion due to stimulation of the subepicardial layers. In these cases, augmentation of function after revascularization is not expected. Because the underlying mechanism, prognosis, and therapy may differ among these conditions, it is crucial to differentiate among dysfunctional myocardial segments that are nonviable and have no potential to regain function, hibernating or ischemic segments in which recovery of function occurs only after revascularization, and myocardial stunning in which function is expected to recover spontaneously. Because combinations of all of these disorders may occur, even in the same segments, caution should be used in interpreting the imaging results.

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Left ventricular function is an important predictor of outcome in patients with coronary artery disease, especially after myocardial infarction.[1–3] In addition to myocardial infarction and scarring, coronary artery disease can lead to left ventricular systolic dysfunction by several mechanisms, including myocardial ischemia, stunning, and hibernation.[4,5] Early identification and treatment of reversible causes of myocardial infarction may lead to improved left ventricular function and a better prognosis.* Acute ischemia may lead to transient regional wall-motion abnormalities of the left ventricle. Even asymptomatic ischemia (silent) that involves only the inner layers of the ventricular wall may lead to impaired function. Moreover, regional myocardial dysfunction may continue several days to weeks after flow is restored to a previously ischemic zone (myocardial stunning).

Chronic myocardial dysfunction may occur in regions with a partial reduction of flow. Although this phenomenon was ascribed to metabolic adaptation to chronic ischemia (myocardial hibernation), chronic dysfunction may be explained by the occurrence of either or both repetitive episodes of ischemia and stunning during daily activity and nontransmural or patchy myocardial necrosis. It has been reported that the presence of necrosis of less than 20% of the myocardial wall is enough to produce hypokinesia because at rest only the inner part of the ventricular wall contributes to contraction and wall thickening. Thus, regional dysfunction may occur at rest even when the midepicardial and subepicardial zones are viable.[6] In addition, in regions where islands of viable myocardium are surrounded by extensive fibrosis, contraction may be precluded or inhibited by the fibrosis. Hence, chronic myocardial dysfunction may persist despite the presence of viable myocardium. These disorders are not mutually exclusive. For example, a zone of viable myocardium overlying a subendocardial infarction may be supplied by a

*See also the editorial by R. O. Bonow, MD, "The Search for Viable Myocardium," on pages 393–396 of this issue.

From the Heart Institute, Good Samaritan Hospital, and the University of Southern California, Los Angeles.

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Reprint requests to Robert A. Kloner, MD, PhD, Director of Research, Heart Institute Research, Good Samaritan Hospital, 1225 Wilshire Blvd, Los Angeles, CA 90017.

ABBREVIATIONS USED IN TEXT

ACE = angiotensin-converting enzyme
ATP = adenosine triphosphate
PET = positron-emission tomography

critically stenotic artery and thus exposed to repeated episodes of acute ischemia, stunning, or hibernation—or a combination of them.

Differentiating viable from nonviable myocardium in noncontracting or hypocontracting segments has prognostic relevance. The presence of viable myocardium in the outer layers of the ventricular wall may prevent ventricular remodeling and infarct expansion after acute myocardial infarction and thus prevent the deterioration of left ventricular function, progression to heart failure, and an increased risk of death.[6] Although the outer layers of the ventricular wall do not contribute to regional function at rest, during exercise these layers may react to increased catecholamine levels, which may augment left ventricular function in patients with subendocardial infarction.[6] Furthermore, the dysfunction of viable myocardium may be reversible and may resolve spontaneously over time (myocardial stunning) or after revascularization (hibernating myocardium). Hence, it is crucial not only to document the presence of viable myocardium, but also to determine whether the augmentation of function is to be expected spontaneously over time or after revascularization.

In this article, we review the clinical relevance, means of detection, and differential diagnosis of the various syndromes that may lead to the dysfunction of viable myocardium.

Stunned Myocardium

Myocardial stunning, or postischemic dysfunction, is defined as the delayed recovery of myocardial function despite the restoration of coronary artery flow to previously ischemic myocardium in the absence of irreversible damage.[7] The major difference between stunning and hibernation or ischemia is that blood flow is normal or near normal in stunning, whereas it is reduced in ischemia or hibernation.[5] Both systolic and diastolic dysfunction have been reported in stunned myocardium.[7] The phenomenon of myocardial stunning was first described in 1975 in conscious dogs with experimentally induced acute ischemia.[8] It has been observed after various types of experimental myocardial ischemia and reperfusion models in several animal species.[9] Only after reperfusion modalities were introduced for the treatment of acute myocardial infarction, however, did the clinical relevance of differentiating stunned from hibernating or infarcted myocardium become apparent. The widespread use of invasive and noninvasive imaging modalities for assessing function, perfusion, and metabolism has resulted in the recognition that reversible dysfunction of viable myocardial regions is more common than previously thought.[7]

Myocardial stunning is probably a multifactorial process. Several mechanisms may be involved in generating this phenomenon. Two major hypotheses have been proposed to explain the cause of postischemic myocardial dysfunction: oxygen free radical generation at the time of reperfusion, abnormal calcium homeostasis, or some combination of the two.[10] The severity and duration of postischemic dysfunction are closely related to the duration and severity of the preceding ischemia. The presence of residual flow to the ischemic zone through collaterals attenuates stunning. Short ischemic episodes lasting less than a few minutes are usually not sufficient to cause stunning and may even result in a transient hypercontractility following reperfusion.[11] After longer episodes of ischemia, a short period of increased contractility has been demonstrated on reperfusion, lasting up to three minutes, followed by a gradual decline of function. This brief phase of recovery may be related to the presence of reactive hyperemia or increased catecholamine levels. The longer the ischemic insult, the greater and more prolonged is the ensuing dysfunction. Thus, brief ischemic episodes as seen during variant angina or balloon occlusion during angioplasty are not usually associated with prolonged stunning, whereas transient myocardial dysfunction following reperfusion therapy for acute myocardial infarction or after a cardiac operation may last for several days.

Myocardial Stunning in Patients

Myocardial stunning in patients reperfused for the treatment of acute myocardial infarction. Numerous studies using various imaging techniques have shown a gradual recovery of regional myocardial dysfunction over ten days to several weeks after successful reperfusion therapy in patients with acute myocardial infarction.[7] Very early reperfusion results in a faster and greater recovery of function relative to reperfusion three to four hours from the start of cardiac pain.[7] There are studies showing that infusing inotropic agents augmented regional and global systolic function, which was more pronounced in patients who were successfully reperfused than in patients in whom reperfusion failed. This reversible regional dysfunction could be shown as early as three days following the reperfusion of acute anterior wall myocardial infarction.[12] Spontaneous delayed recovery of function may, however, be related to a gradual improvement of myocardial perfusion by either delayed recanalization or the recruitment of collaterals. Hence, the distinction between hibernation and stunning cannot always be made from these studies.[7]

Myocardial stunning in unstable angina. Unstable angina is a heterogeneous syndrome, spanning from a new occurrence of effort angina to severe angina occurring at rest. Furthermore, the extent of luminal occlusion that is produced by an intracoronary thrombus fluctuates over time. A patient with unstable angina may have repeated episodes of ischemic pain, silent ischemia, and reperfusion. Hence, transient regional dysfunction may be related to active ischemia (painful or silent) or stunning. Thus, the repeated simultaneous demonstration of reduced regional function in a normally perfused segment

is mandatory for the diagnosis of stunning and ruling out chronic or acute ischemia as the cause of the dysfunction. Most of the previous studies showing an improvement in the regional wall-motion score between admission and a later time point, both with conservative therapy, after angioplasty, or following coronary artery bypass grafting, failed to fulfill these criteria.[7] In one study, a delayed recovery of regional wall-motion abnormalities was demonstrated after chest pain resolved in six patients with unstable angina pectoris. The authors noted that in shorter ischemic episodes (about 10 minutes), the recovery was almost complete two hours after the chest pain, whereas longer episodes of pain resulted in delayed recovery over more than 24 hours.[11] As mentioned earlier, however, because no direct evidence was presented of the restoration of flow after the pain resolved, persistent (silent) subendocardial ischemia or hibernation as the cause of dysfunction could not be ruled out.

Myocardial stunning in variant angina. The evidence for myocardial stunning after episodes of vasospastic (Prinzmetal's) angina is sparse. This is probably because most ischemic episodes are too short to produce stunning.[7]

Myocardial stunning after exercise. Immediately following exercise-induced ischemia, there is abatement in regional wall-motion abnormalities, probably due to the increased levels of catecholamines. In some segments, however, a gradual deterioration of function appears in previously ischemic zones that may be detected over the following 10 to 20 minutes. This phenomenon is seen especially in patients who suffered from severe and prolonged ischemia during effort—that is, those with multivessel disease and severe luminal narrowing. Myocardial stunning in these cases may last as long as 30 to 45 minutes.[13,14]

Myocardial stunning after coronary angioplasty. The occlusion periods by balloon inflation, as commonly practiced, are probably too short to induce prolonged systolic stunning. Indeed, a prompt return of systolic function has been observed after angioplasty, although diastolic dysfunction may persist.[7] When balloon occlusions were extended to four to seven minutes, however, a delayed recovery of regional wall motion and thickening was observed that lasted as long as three days.[7]

Myocardial stunning after cardiac surgery. Numerous studies reported that regional and global myocardial function may be depressed for 24 to 48 hours after cardiac surgery.[5,7]

In the course of cardiac transplantation, the heart undergoes periods of global ischemia followed by reperfusion. Thus, a component of myocardial stunning should be expected. Indeed, transient hemodynamic instability is commonly observed in the period immediately after transplantation.[7]

Therapy for Myocardial Stunning

According to experimental models, myocardial stunning can be prevented by administering antioxidative agents just before reperfusion. In the clinical setting, however, the goal would be to prevent severe and prolonged stunning episodes that follow prolonged ischemic episodes as seen in acute myocardial infarction or after cardiac surgery.[15] Several authors have reported that administering allopurinol, a blocker of free radical production, improved cardiac performance and reduced cardiac complications in patients who underwent coronary artery bypass grafting.[16] These studies included a small number of patients, however. Till now, no other controlled clinical trial has documented the efficacy of antioxidants in patients with myocardial ischemia. The use of recombinant human superoxide dismutase and intravascular perfluorochemical emulsion (Fluosol) failed to prevent reperfusion injury and stunning following reperfusion therapy for acute myocardial infarction.[17,18]

Calcium antagonists have a possible role in the prevention of stunning by blocking the hypercalcemic phase and by their free radical–scavenging effect.[19(p281)] Various experimental models of global or regional brief myocardial ischemia and reperfusion have shown that calcium antagonists given especially before occlusion, but also during reperfusion, enhance the recovery of contractile function. But the results following long ischemic episodes are conflicting.[19] The effect of calcium antagonists on myocardial stunning has been evaluated only in small clinical trials. Adding nifedipine or diltiazem to cardioplegic solutions resulted in improved myocardial metabolism and hemodynamic status.[19] The use of calcium antagonists lessened myocardial stunning induced by prolonged balloon inflation during angioplasty.[20]

The evidence for the efficacy of β-blockers to enhance the recovery of postischemic dysfunction is equivocal. Several studies have shown that administering stable analogues of prostacyclin enhanced the recovery of myocardial function on reperfusion. Although the use of angiotensin-converting enzyme (ACE) inhibitors has been shown to enhance the recovery of function following ischemic-reperfusion insult, the mechanism is not clear. The sulfhydryl-containing agents captopril and zofenopril have been shown consistently to ameliorate stunning, possibly by their antioxidant properties. Even other ACE inhibitors that do not contain the sulfhydryl group are, however, effective in some experimental models of stunning.

There is some experimental and clinical evidence that the use of ubiquinone (coenzyme Q_{10}) augments the recovery of function after an ischemic insult. A small randomized clinical study demonstrated better preservation of the myocardium and enhanced recovery of function after cardiac surgery using hypothermic cardioplegic arrest in patients pretreated with ubiquinone.[15]

Nicorandil, a nicotinamide nitrate that is capable of opening the adenosine triphosphate (ATP)–sensitive potassium channels, has been shown in several animal models to attenuate myocardial stunning when administered before ischemia or added to the cardioplegic solution.[21,22] Clinical studies on the prevention of myocardial stunning with the use of nicorandil have not yet been published, however.

The prevention of stunning in a patient with prolonged ischemia (myocardial infarction or cardiac operation) is still not feasible. In cases with clinical heart failure following reperfusion, however, a transient augmentation of global and regional function is possible by infusing various positive inotropic agents. Various β-mimetic agents have been reported to enhance contractility and improve diastolic relaxation in an ischemic-reperfused zone, without further depletion of ATP stores.[15] Because of the decrease of the β-adrenergic receptors with continued stimulation, however, the effect is lost after 24 hours of infusion. Hence, this type of therapy may be considered to support the stunned myocardium and make it contract, but probably should not be thought of as a primary therapy for stunning.

Hibernating Myocardium

Hibernating myocardium is defined as the persistent dysfunction of viable myocardium at rest due to an ongoing reduction of myocardial perfusion. The hallmark of myocardial hibernation is a parallel reduction of myocardial perfusion and function. By definition, this myocardial dysfunction can be reverted with the restoration of coronary artery flow.

Myocardial Hibernation in Patients

Despite controversy concerning the underlying mechanisms, the phenomenon of the recovery of regional and global left ventricular function at rest after revascularization in patients with chronic left ventricular dysfunction suggests that many myocardial regions that are asynergic before revascularization represent viable myocardium.[23–26] As many as 42% of patients with coronary artery disease have hibernating segments that improve after revascularization.[27,28] Some studies suggest that the improvement in wall motion occurs immediately,[26,29,30] whereas others demonstrate a more gradual restoration of function, suggesting that either the metabolic and structural changes that occur during chronic ischemia recover slowly from the hibernation state or that there is a component of stunning on reperfusion.[31,32]

Of interest, a substantial proportion of patients with severe heart failure due to ischemic cardiomyopathy and referred for cardiac transplantation have hibernating myocardium, and their cardiac function improves considerably after coronary artery bypass grafting.[33,34]

Pathophysiology

Unlike other ischemia-related syndromes, such as myocardial stunning, myocardial hibernation was initially defined based on clinical observations and not on observations during experiments with animals. In 1973 a notable incidence of improved segmental myocardial wall motion after coronary artery bypass grafting was reported.[35] In 1985, in a commentary on the results of coronary artery bypass surgery trials, the concept of metabolic adaptation to chronic ischemia as a protective mechanism was suggested and the term "hibernating myocardium" was used.[36] Rahimtoola hypothesized that the myocardium slows down its function and metabolism to survive when the oxygen supply is reduced.[37] There is a debate whether the myocardium really "hibernates,"[38] especially because no good animal model has been found that can mimic prolonged hibernation. The issue is whether hibernating myocardium represents an active process of inhibited metabolic demand due to severe, ongoing, silent low blood flow or repetitive stunning following discrete episodes of ischemia.[27,38,39]

The mechanism of regional dysfunction in patients with coronary artery disease was investigated in one study.[40] Patients were selected who had total occlusion of the coronary artery with corresponding myocardial dysfunction and in whom myocardial perfusion to the area of dysfunction depended entirely on collateral blood flow supply. The investigators found substantial morphologic abnormalities in myocardial tissue specimens obtained at the time of bypass grafting in dysfunctioning collateral-dependent segments. These abnormalities included cellular swelling, the loss of myofibrillar content, and the accumulation of glycogen. On positron-emission tomography (PET) study, however, these collateral-dependent but dysfunctional myocardial segments had nearly normal resting flow and oxygen consumption. Based on the PET studies, the dysfunctional segments did not fulfill the conventional criteria for "hibernation." The authors concluded that repetitive stunning rather than long-term hibernation was responsible for myocardial dysfunction.

The morphologic changes of the hibernating segments have recently been documented in patients undergoing a coronary artery bypass operation. Biopsies from dysfunctional but viable zones have shown a loss of sarcomeres, abundant glycogen granules, rough endoplasmic reticulum and mitochondria, tortuous nuclei, and an increase in connective tissue strands. These alterations have suggested that myocytes may "de-differentiate" or atrophy from the long-term reduction of flow, disuse, or both. The same phenomenon of "de-differentiation" and atrophy occurs when a limb muscle is placed in a cast or sling for several weeks. These morphologic changes may explain the observation that in some studies, the restoration of function following revascularization is slow. The number of affected cells was greater in endocardial than in epicardial portions.[31,32,41] Thus, the severity of the structural changes in chronically ischemic myocardium varies considerably, and perhaps, the reversibility and the rate of restoration of the structural changes and dysfunction are dependent on the severity of derangements.

Therapy for Myocardial Hibernation

The ultimate therapy for hibernating myocardium is prompt revascularization by either percutaneous techniques or coronary artery bypass grafting. It has been suggested that hibernating myocardium acts as an "unstable substrate" for further ischemic events[42] and that revascularization will result not only in improved ventricular function but also in a better prognosis.[33–35]

Although global and regional function may be aug-

mented by the use of positive inotropic agents, at least transiently, the results of experiments with animals raise concern that inotropic stimulation in the presence of severe hibernation may interfere with the metabolic equilibrium and may precipitate ischemia and infarction.[43] Therefore, although inotropic stimulation may be used to demonstrate functional reserve and viability during diagnostic tests (see later), the long-term use of positive inotropic drugs may be deleterious. This may partially explain the deleterious effects of several inotropic agents on survival of patients with heart failure and coronary artery disease.

Identification of Viable Myocardium

The current standard for myocardial viability is the augmentation of function over time either spontaneously (acute ischemia and myocardial stunning) or after revascularization (ischemia and hibernation). Methods for detecting viability may focus either on simply detecting viability (before revascularization is attempted) or, as in most recent studies, on predicting functional recovery. Ventricular function is a major determinant of survival in patients with coronary artery disease, and available data suggest that an improvement in ventricular function will translate into a better prognosis. Therefore, it is essential to identify not only dysfunctional segments with viable myocardium, but most important, segments that have the potential to regain function after revascularization. In particular, it is crucial to identify the patients with hibernating myocardium who may benefit from coronary revascularization. To help determine this, clinicians need evidence of viability of the dysfunctional regions, an assessment of perfusion at baseline and during stress to these zones, and a prediction of whether interventions will result in augmenting function.[6] Although revascularization is usually considered for those segments with the potential to regain function, there may be substantial limitations in using this as the only marker for the efficacy of revascularization. Other important end points might include survival, functional capacity, quality of life, and electrical stability.

Assessing Myocardial Viability

Evidence of myocardial viability usually relies on the demonstration of perfusion (even if considerably reduced) or the uptake of various metabolic tracers by the myocytes. The demonstration of contractile reserve may be another indication of viability. As mentioned earlier, however, not all viable regions may have contractile reserve, and the augmentation of function may be the result of the enhanced contraction of normal myocardium adjacent to a permanent scar.[6]

Electrocardiogram. The absence of Q waves in the territory of dysfunctional myocardium has been suggested as a marker of viability.[44] This method is not specific, however. Many myocardial segments showing Q waves on an electrocardiogram are still viable.[44] Although early and persistent T wave inversion after reperfusion therapy for acute myocardial infarction has been reported to be a sign of myocardial viability and stunning, these electrocardiographic changes are not sensitive or specific. New or more ST segment elevation and pseudonormalization of negative T waves in patients after Q wave infarctions during low-dose dobutamine infusion have been associated with viability and contractile reserve.[45]

Thallium myocardial imaging. Thallium myocardial imaging is used clinically to assess myocardial perfusion and viability.[46] About 50% of myocardial segments with persistent or fixed defects on conventional stress imaging and imaging after three to four hours of the redistribution of thallium (thallous chloride TL 201) are falsely characterized as scar, however.[46] Three clinical approaches can be used to detect viability: stress redistribution with additional delayed redistribution imaging, stress-redistribution-reinjection imaging or rest-redistribution imaging.[47,48] By readministering ^{201}Tl-thallous chloride at rest, nearly 50% of the defects that seem to be fixed at four hours of redistribution are reversible.[46] The method of rest redistribution may be more suitable for patients with ischemic cardiomyopathy with severe left ventricular dysfunction who cannot exercise or who have contraindications to stress testing. The sensitivity of this technique is low, however. A substantial proportion of segments that show fixed perfusion defects on rest-redistribution thallium scans improved considerably following revascularization.[46]

The addition of quantitative analysis has been found to enhance the sensitivity for predicting viability in patients with fixed thallium defects.[47,48] Viability is likely to be present if delayed images show only a mild or moderate defect (>50% in thallium activity relative to activity in the normal zone).[46,48] The spatial differentiation between the subendocardial and subepicardial layers of the myocardium by thallium is poor. Thus, the use of "more than 50% thallium activity" would not differentiate between viable segments with the potential for the recovery of function and segments with an admixture of fibrosis, scar, and normal myocardium that would not improve on reperfusion.[46] It should be remembered, however, that immediately on reperfusion, there may be a transient hyperemic state, which could lead to an excessively high thallium uptake, even in necrotic zones. Hence, administering thallium in the first few hours after reperfusion in patients with acute myocardial infarction may overestimate the amount of viable myocardium.[47] Necrotic myocardium cannot retain thallium; hence, there is early washout from the necrotic zones that can be shown with late redistribution imaging.[47]

Technetium Tc 99m sestamibi. Technetium Tc 99m sestamibi has been suggested as an excellent agent to use for the simultaneous demonstration of impaired function coupled with normal perfusion in stunned myocardium. Its use, however, may have limitations in patients with hibernating myocardium. The uptake of ^{99m}Tc-sestamibi is flow dependent. As ^{99m}Tc-sestamibi does not redistribute, its use tends to underestimate the magnitude of viable hypoperfused myocardium compared with that of thallium.[46]

Positron-emission tomography. Positron-emission tomography has evolved as the noninvasive standard for determining viability. The PET criterion for viability is the demonstration of glucose metabolism in hypofunctioning myocardium using the radiolabeled glucose analogue fludeoxyglucose F 18.[46] The positive predictive value is as high as 85% and the negative predictive value as high as 92%.[34,49,50] Positron-emission tomography provides enhanced image resolution and routine correction for body attenuation, thereby overcoming the two major limitations of thallium imaging. The use of this technique, however, similar to that of thallium imaging, overestimates the extent of viable myocardium soon after acute myocardial infarction.[47]

Although PET technology may be superior to thallium imaging, it is expensive and not readily available. Thallium imaging is widely available for clinical use and provides a less expensive alternative to PET assessment of regional metabolic activity. It has been reported that the predictive accuracy of thallium reinjection studies approaches that of PET.[47]

Myocardial contrast echocardiography. The evaluation of myocardial perfusion and function with the intravenous administration of a contrast medium is under investigation, and this technique is not yet clinically available. Myocardial contrast echocardiography has recently been suggested as a promising method for evaluating flow reserve and myocardial viability and predicting the restoration of myocardial function after revascularization.[51] The technique of myocardial contrast echocardiography allows the simultaneous assessment of function, perfusion, and microvascular integrity.[6] Moreover, myocardial contrast echocardiography enables spatial resolution to assess microvascular integrity and perfusion in the various layers of the ventricular walls. For example, this technique may allow the demonstration of a fixed subendocardial perfusion defect (subendocardial infarction) overlaid by normally perfused midepicardial and subepicardial layers as the underlying mechanism for regional dysfunction at rest with contractile reserve. Theoretically, this technique may also show that the outer layers overlying subendocardial infarction are exposed to ischemia on stimulation, and thus a component of irreversible subendocardial infarction combined with hibernation or repetitive ischemia and stunning in the subepicardial layers may be responsible for the dysfunction. The predictive value of myocardial contrast echocardiography was recently shown to be comparable to that of dobutamine stress echocardiography in hypokinetic segments.[52] In akinetic segments, however, contrast echocardiography may demonstrate perfusion in areas that do not recover function after revascularization. In akinetic segments, dobutamine stress echocardiography is more accurate.

Assessing Contractile Reserve

Assessing the presence of contractile reserve, either during nitroglycerin administration,[53] after extrasystolic potentiation,[54] or during low-dose sympathomimetic infusion,[55] dipyridamole testing,[56] or immediately after exercise,[57] has been proposed to identify viability in patients with regional myocardial dysfunction.

Regional wall motion at baseline and during intervention can be assessed either by contrast ventriculography or by noninvasive techniques such as radionuclide ventriculography or echocardiography (transthoracic or transesophageal).[58,59] Because echocardiography is a relatively inexpensive technique that enables a clear demonstration of regional contraction and wall thickening in the various segments of the heart, it is emerging as an extremely useful modality for evaluating contractile reserve and myocardial viability.[60–62] The response of regional ventricular segments to various doses of dobutamine infusion may indicate the underlying mechanism of dysfunction. Normal segments that receive normal perfusion will show normal contractility at baseline and the augmentation of contractility during infusion in a dose-dependent manner. Stunned regions that have normal or near-normal perfusion will show hypokinesia or akinesia at baseline with a dose-dependent augmentation of function on dobutamine infusion. But if the region has residual stenosis of more than 50% and may be hibernating, the use of a low-dose (5 to 10 μg per kg per minute) dobutamine infusion may result in increased contractility, whereas higher doses (20 to 40 μg per kg per minute) may induce ischemia and, thus, a deterioration of contractility. Some investigators suggest that this biphasic response is a signature of hibernation. In patients with a severely reduced blood supply, however, even low doses of dobutamine may induce ischemia, and hence, no augmentation of function will be observed. This may explain the lower sensitivity of dobutamine echocardiography for detecting hibernating myocardium in segments supplied by critically stenotic arteries. Moreover, dobutamine stress echocardiography cannot differentiate between stunning with reduced flow reserve, acute ischemia, and chronic hibernation. This differentiation should rely on the simultaneous demonstration of perfusion by either coronary angiography, radionuclide techniques, or myocardial contrast echocardiography.

Conclusion

Because the prognosis is highly dependent on left ventricular function, it is crucial to differentiate between dysfunctional myocardial segments that are viable and infarcted or fibrotic segments that have no potential to recover function. Moreover, it is essential to distinguish between stunned myocardial segments, which will show a spontaneous recovery of function even without intervention, and regions subjected to acute ischemia or a long-term reduction of blood flow (hibernation), in which the recovery of function will occur only after blood flow is restored. Note that the demonstration of viability or functional reserve following exercise or stimulation is not necessarily sine qua non with the recovery of function following revascularization. For example, segments with subendocardial infarction or extensive

fibrosis may show the augmentation of function on stimulation because of recruitment of neighboring viable cells, but their systolic function, at least at rest, will not improve on revascularization, and a substantial percentage of segments without evidence of viability will have improved function after revascularization. There is a need for improving our ability not only to differentiate viable from nonviable muscle, but also to identify the underlying mechanism of dysfunction and to predict which segments will improve function after reperfusion.

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Epitomes

Important Advances in Clinical Medicine

Obstetrics and Gynecology

W. Gordon Peacock, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in obstetrics and gynecology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Obstetrics and Gynecology of the California Medical Association, and the summaries were prepared under the direction of W. Gordon Peackock, MD, and the panel.

Prematurity—Steroids for All

OVER THE PAST DECADE, perinatal mortality in the United States has fallen to rank a dismal 22nd in the world. The source of this national problem is our extraordinary high rate of preterm births. About 8% of births in the United States occur before 37 weeks of gestation. This has driven health professionals, government agencies, and entrepreneurs to develop new and different measures to prevent or ameliorate the consequences of prematurity. Unfortunately, few of the new approaches have lived up to hopes: screening tools for high-risk pregnancies, home uterine activity monitors, and tocolytic drugs—medications used to treat contractions—have all been mired in controversy over how much benefit, if any, they offer. Often overlooked is the real breakthrough of administering corticosteroids to a woman to advance the pulmonary maturation of her preterm infant.

In the past 24 years, more than 20 randomized, double-blind, controlled trials have shown that prenatal corticosteroid use leads to a major reduction in the incidence of the respiratory distress syndrome, the major cause of neonatal mortality and morbidity. The degree of reduction is dramatic: following an optimal course of betamethasone sodium phosphate, 12 mg given intramuscularly every 12 or 24 hours for two doses and the delay of delivery for 48 hours from the first dose (good for 7 days), the incidence of the respiratory distress syndrome is reduced by 67%. The incidence of the second leading cause of neonatal morbidity, intracranial hemorrhage, is reduced by 50%, that of necrotizing enterocolitis by 65%, and neonatal deaths overall by nearly 40%.

Side effects have been surprisingly limited despite the fact that these are large doses of steroids—12 mg of betamethasone is equivalent to 60 to 80 mg of prednisone. The incidence of maternal and neonatal infections is not increased. Adrenal suppression has been reported only in isolated cases. Long-term (≥10 years) follow-up studies of exposed neonates have shown no ill effects. The early association with maternal pulmonary edema was later found to be related to the use of tocolytic drugs and injudicious fluid administration. The only caution is the use of betamethasone in women with diabetes mellitus. Insulin requirements may double. Careful monitoring of plasma glucose levels to prevent diabetic ketoacidosis is mandatory.

There is a wide range of benefits: fetuses as small as 500 grams and as old as 34 weeks are notably benefited. Fetuses with preterm rupture of the membranes have a reduced incidence of the respiratory distress syndrome of 50% from corticosteroid administration. Contrary to the results of initial studies, infants of women with hypertensive disorders respond well to the use of steroids and, when monitored closely, have no increased risk of stillbirth. The recent development of postnatal surfactant administration to infants with respiratory distress has not rendered the use of steroids obsolete. The benefits of corticosteroid use have been clearly shown to be additive to those of surfactant use.

This drug has been intensively studied. The real question is, why is it so little used? Some estimates suggest that only 30% to 40% of preterm infants receive steroids before birth. To address this issue, the National Institute of Child Health and Human Development recently sponsored a consensus development conference that strongly supported the widespread use of this treatment. The data in their document substantiating the benefits of prenatal corticosteroid use are overwhelming. A more widespread use could save more than $35 million each year.

Which mothers should receive corticosteroids? If a complication that could lead to preterm birth develops in a woman at any point between 24 and 34 weeks of gestation, one of the first medications she should receive is 12 mg of betamethasone intramuscularly (repeated once in 12 or 24 hours). These conditions include preterm labor with cervical change; a need for parenteral tocolytic

drugs; preterm rupture of the membranes; vaginal bleeding from placenta previa, abruption, or marginal sinus rupture; or admission to the hospital for medical complications such as preeclampsia.

ELLIOTT K. MAIN, MD
San Francisco, California

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Intracytoplasmic Sperm Injection

A DEFICIENT NUMBER OF normally formed and active spermatozoa is thought to be responsible for as many as 40% of cases of human infertility; yet, with the possible exception of varicocele repair, not a single effective treatment to increase male fertility has appeared since Leeuwenhoek first viewed sperm through his primitive microscope 300 years ago. Artificial insemination using the sperm of the husband was first described in the 19th century and widely applied despite a lack of evidence of its efficacy. In the past ten years, efforts to concentrate sperm and place them closer to the egg by direct insemination into the uterus have met with modest success. For men with sperm concentrations of less than 5 million per ml (normal, 20 million per ml) or with abnormalities of motility or structure, however, only in vitro fertilization (IVF) has been available. Because sperm from infertile men are often deficient in their capacity to penetrate the zona pellucida that surrounds the egg, even IVF results have been generally disappointing as a treatment of male factor infertility.

In an effort to allow the sperm to breach the zona barrier, various techniques were developed that involved cutting or mechanically disrupting the zona or attempting to create openings by introducing acids or enzymes. These methods not only damaged the oocytes or blastomeres, but they often allowed more than one sperm to enter the egg (polyspermia). The first technique to achieve some success involved placing a single motile sperm in the perivitelline space with a thin glass micropipette and was known as subzonal insertion, or SUZI. In 1992, while performing SUZI in Brussels, Van Steirteghem inadvertently injected a sperm directly into the egg cytoplasm and noted that his fortuitous error resulted in an apparently normal fertilization. His report of four pregnancies by this method reestablished the concept of intracytoplasmic sperm injection (ICSI), a technique that had been tried but abandoned by North American investigators four years earlier.

Since 1992, ICSI has replaced all other techniques in the treatment of severe male infertility by allowing for pregnancy in cases with markedly reduced numbers of normal sperm. After exogenous gonadotropin stimulation, several oocytes are removed from their follicles by needle aspiration using transvaginal ultrasonographic guidance. In the laboratory, a single sperm is injected into the cytoplasm of each oocyte with an extremely fine glass needle. With experience, fertilization will occur in about two thirds of injected eggs, and only about 5% will be lost through mechanical trauma. Intracytoplasmic sperm injection adds about $1,000 to the cost of a $6,000 to $8,000 IVF cycle and achieves the same pregnancy rate as when IVF is performed with normal sperm, about 20% to 40% per cycle. More recently, ICSI has been extended to the treatment of men who have zero sperm counts as long as sperm can be microsurgically removed from the epididymis, such as in men with congenital absence of the vas deferens. The latest finding is that the use of even round-headed sperm (which lack an acrosome) can result in fertilization, thus allowing for the use of "immature" sperm cells recovered by biopsy directly from the testis itself.

Although concerns have been raised concerning the unintentional selection of genetically abnormal sperm, the effects of physical damage to the oocytes, and the transmission of genetic diseases that are linked to male infertility (such as cystic fibrosis and congenital absence of the vas), the first several hundred babies delivered after ICSI have not shown an increase in congenital malformations. So far, ICSI has not only proved to be a stunning advance in the treatment of male infertility, it is also a powerful tool to study the microdynamics of human fertilization.

ROBERT D. NACHTIGALL, MD
San Francisco, California

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Androgen Replacement in Postmenopausal Women

THE BENEFITS OF estrogen replacement in postmenopausal women are well established. Estrogen replacement decreases the risk of cardiovascular disease, protects against osteoporosis, reverses atrophic genital changes, eliminates vasomotor symptoms, and improves cognitive function. The most common side effect of estrogen replacement is abnormal bleeding. Endometrial hyperplasia and adenocarcinoma are rare if appropriate doses of progestin are administered. Most current studies do not show that

the risk of breast cancer is substantially increased by estrogen replacement, although further investigations are needed.

Increasing attention is being paid to the role of androgen replacement in postmenopausal women. The thought that estrogen was exclusively a female hormone and that testosterone was a male hormone is no longer valid. In women, testosterone and androstenedione are produced by both the premenopausal and postmenopausal adrenal glands and ovaries. Androstenedione is a steroid precursor that is converted to estrogen and testosterone in peripheral tissue. Estrogen production in postmenopausal women is almost exclusively the result of peripheral aromatization of androstenedione from the adrenal glands. Androstenedione production decreases by 50% when a woman enters menopause. Most of this decrease is the result of decreased ovarian production of androstenedione. Testosterone production decreases by close to 30% in menopause. Most of this decrease is due to a fall in nonovarian production of testosterone.

Both estrogen and androgen are thought to play crucial roles in female sexual behavior. In the female brain, testosterone receptors are located in areas involved with libido and emotions. Testosterone deficiency has been shown to result in a loss of libido. Administering testosterone combined with estrogen is superior to the use of either estrogen alone or placebo in the treatment of postmenopausal women with a loss of libido. The benefits of testosterone use seem to be greater in women who undergo surgical menopause than in those who undergo natural menopause. This finding is consistent with the knowledge that postmenopausal ovaries continue to produce testosterone at premenopausal levels even though the production of androstenedione decreases considerably.

Administering estrogen and androgen may have a synergistic effect on improving mood and sense of well-being in postmenopausal women. This is important because depression is encountered twice as often in women as in men. Controlled studies involving women who had undergone surgical menopause by total abdominal hysterectomy and bilateral salpingo-oophorectomy have shown that testosterone supplementation has a positive effect on energy level, sense of well-being, and appetite. When these women are given estrogen combined with testosterone, they have fewer somatic complaints such as hot flushes, cold sweats, and headaches than when they are given either estrogen alone or placebo. They also have fewer complaints such as fatigue, irritability, nervousness, depression, poor memory, insomnia, inability to concentrate, crying spells, panic attacks, and indifference when treated with estrogen combined with testosterone than when treated with estrogen alone or placebo. It has not yet been established whether estrogen combined with testosterone offers postmenopausal women any additional protection against osteoporosis beyond that which is gained from estrogen administration alone.

Testosterone can be administered orally, parenterally by injection, or by subcutaneous pellets. Oral esterified estrogens or conjugated estrogen combined with methyltestosterone are most commonly used. These formulations contain 1.25 to 10 mg of methyltestosterone per tablet and can be administered cyclically in a regimen identical to that of estrogen administered alone. As is the case with the use of estrogen alone, women must be given progestin in an appropriate regimen to protect against endometrial hyperplasia and carcinoma unless they have undergone hysterectomy.

The possible side effects of testosterone administration, which include hirsutism, skin oiliness, and acne, have an incidence of less than 1%. Although rare, hirsutism may be encountered in Hispanic or Mediterranean women. These women can be managed with the addition of oral spironolactone, 100 mg each day. Changes in voice and clitoromegaly are extremely rare with low doses of testosterone. There have been concerns that the use of testosterone might result in adverse changes in cholesterol, high-density lipoprotein, low-density lipoprotein, and triglyceride levels that would blunt or reverse the protective effects of estrogen against cardiovascular disease. Most studies have found that when administered in low doses, testosterone had no significant adverse effects on the lipid profile.

Further investigations concerning androgen replacement in postmenopausal women are necessary. There currently are insufficient data to support androgen replacement in all postmenopausal women. It appears that low-dose androgen replacement in postmenopausal women is safe, however. The addition of androgen to estrogen replacement may be useful in postmenopausal women who have a loss of libido and those who have persistent somatic or psychological symptoms despite being treated with high-dose estrogen replacement. In particular, women who have undergone surgical menopause may be candidates for androgen replacement therapy.

HOMER G. CHIN, MD
San Diego, California

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Adolescent Contraception

RECENT STUDIES have again shown that rates of sexual activity among teens in this country are not substantially different from these rates in other developed western countries. About a third of adolescent women in their freshman year of high school have been sexually active, and nearly two thirds of high school senior-aged women have. By the age of 19, the average North American man has had 5.11 partners. Adolescent pregnancy rates in the United States, however, are severalfold higher than most

other countries. One of the keys for this discrepancy lies in our collective reluctance to discuss sexuality issues with or provide contraception to adolescents. Classic studies show that teens are interested in these topics; more than two thirds want to talk to their physicians about sexually transmitted diseases, contraception, and other sexually related issues. Because of their reluctance to ask direct questions and physicians' lack of initiative, however, it is far more likely a teen will wind up discussing menstrual problems with her physician instead.

Effective communication is the key to providing contraception to teens. This is challenging for physicians because mental maturity does not necessarily keep pace with physiologic development in adolescents. Teens are often concrete thinkers, focused on their physical appearances, and dedicated risk takers attempting to break away from authority figures. Ignoring these properties leads to failure in even the best-intentioned programs. For example, the "Just say no" message conveyed in the "secondary virginity" program promoted by the federal government in the late 1980s and early 1990s to help teen mothers was notably ineffective. More effective programs individually tailor the message of abstinence to each teen, provide concrete techniques to enable an adolescent to say no, and help create alternatives for tempted teens.

The most common form of birth control for adolescents long term is oral contraception. Among teens, the average failure rate for birth control pills is about 8%, but with more consistent use, the rates can be substantially lower. Incentives to better use can be found in the many noncontraceptive benefits provided by oral contraceptive pills. Teens whose dysmenorrhea was reduced with the use of oral contraceptive pills were eight times more likely to be consistent pill users. New Food and Drug Administration (FDA) decisions to include acne as a labeled indication for one type of oral contraceptive pill should broaden their appeal. Pregnancy risks can be reduced for women of all ages by shortening the placebo period. The risk of pregnancy is greatest after seven days without hormones. Women forgetting the last pills in their previous packages or starting a new package late are most vulnerable. To overcome this, women should take the placebo pills only until their menses start (or day 4 of the sugar pills). For teens with active lives (such as athletes), menses can be delayed by "bicycling" or "tricycling" their oral contraceptive pills—that is, taking the active pills in two or three packages without any intervening placebos. If the fear of a pelvic examination prevents an adolescent from seeking oral contraceptive pills, the procedure can be delayed for several months in an otherwise healthy young woman.

The long-acting progestin methods—Norplant and depot medroxyprogesterone acetate (DMPA or Depo-Provera)—are convenient, easy to use, and well tolerated by teens. As a result, they have failure rates of less than 1% and high continuation rates. Several studies of high-risk adolescents have shown one-year continuation rates for implants of more than 80% to 90% compared with 50% for oral contraceptives. The use of DMPA offers more privacy. Adolescents need to be counseled that initially spotting and irregular bleeding occur, but that over time, Norplant users tend to resume normal menses and medroxyprogesterone users usually have amenorrhea. Other hormone-related changes may also occur, and the patient should understand and be willing to accept them before she starts therapy.

Condoms are the method most frequently used at first intercourse, and they play a critical role in reducing the risk of acquiring or transmitting sexually transmitted diseases (STDs) when combined with other methods. Unfortunately, studies show that with teens, condoms alone as a method of contraception have a typical failure rate of about 20%. Barrier users need to understand that the method must be used with every act of intercourse before genital contact. Role playing with providers to learn how to ask their partners to use condoms can improve usage rates—both for pregnancy and STD risk reduction. For young women, vaginal contraceptive foam and condom are easily and discreetly carried in their wallets.

Other options exist for teens. Some older parous teens in stable, mutually monogamous relationships benefit greatly from the efficacy and ease of an intrauterine device, especially the T 380A copper IUD, which is approved for ten years of continuous use. Teens often use sexual practices for birth control (coitus interruptus) and for hymenal preservation (rectal and oral sex). Some of these practices should be discouraged because of infection risks.

The single most important option we can provide teens is emergency contraception with birth control pills. This has recently been approved by the FDA Advisory Board for both safety and efficacy. The need for emergency contraception in teens is well established. Studies show that 25% of college coeds are forced to have sex at least once during their four years of higher learning. Very young sexually active teens are often victims of sexual abuse. Middle teens may succumb to momentary passion. For each of these scenarios, the ability to prevent the exposure to sperm from translating into an unplanned pregnancy can make a pivotal contribution to a teen's lifetime potential. Recent studies show, however, that fewer than 10% of US clinicians informed their patients of the availability of emergency contraception. Standard emergency contraception includes administering a dose of the com-

TABLE 1.—*Emergency Contraception (EC) With Oral Contraceptives**

EC	*Within 72 Hours tablets, No.*	*12 Hours Later tablets, No.*
Ovral	2	2
Lo/Ovral, Nordette, Levlen	4	4
Triphasil-21, Tri-Levlen 28 (yellow tablets)	4	4

*Ovral (Wyeth-Ayerst Laboratories) tablets contain 0.5 mg of norgestrel and 0.05 mg of ethinyl estradiol. Lo/Ovral (Wyeth-Ayerst Laboratories) tablets contain 0.3 mg of norgestrel and 0.03 mg of ethinyl estradiol. Nordette-21 (Wyeth-Ayerst Laboratories) tablets contain 0.15 mg of levonorgestrel and 0.03 mg of ethinyl estradiol. Levlen 21 (Berlex Laboratories) tablets contain 0.15 mg of levonorgestrel and 0.03 mg of ethinyl estradiol. Triphasil-21 (Wyeth-Ayerst Laboratories) tablets contain 0.05 mg of levonorgestrel and 0.03 mg of ethinyl estradiol. Tri-Levlen 28 (Berlex Laboratories) yellow tablets contain 0.125 mg of levonorgestrel and 0.03 mg of ethinyl estradiol.

bination of norgestrel and ethinyl estradiol (Ovral, 2 tablets) within 72 hours, followed by two more tablets 12 hours later. Other levonorgestrel- and norgestrel-containing pills may be substituted if the dosage is adjusted (Table 1). Over-the-counter antiemetics help control side effects.

Single-cycle pregnancy rates with emergency contraception are reduced to 2%, which represents a 75% reduction in pregnancy risk. There is now a toll-free emergency contraception hotline operated by the Office of Population Research at Princeton University for patients and professionals. This number is (800) 584-9911 for information about providers of emergency contraception.

ANITA L. NELSON, MD
Manhattan Beach, California

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Managing Viral Exposure During Pregnancy

THE MANAGEMENT OF viral exposure and disease during pregnancy presents many unique challenges because of possible effects on both a woman and her developing fetus. Maternal rubella infection is a classic example of this. In 1984, before the use of the rubella vaccine, a major epidemic of rubella infection occurred in the United States. During that year, about 20,000 new cases of the congenital rubella syndrome and 11,000 pregnancy losses due to rubella infection occurred in the United States. Certain viruses, such as varicella, may also cause more severe maternal disease during pregnancy. Varicella pneumonia is a relatively common, potentially life-threatening complication of varicella infection during pregnancy.

For most viral diseases, the diagnosis in a pregnant woman rests on serologic testing. Many women with proven viral infection report few, if any, symptoms of infection. Diagnosis is made by demonstrating viral-specific immunoglobulin (Ig) M or a fourfold titer change in specific IgG levels. Routine serologic testing in the United States is currently recommended only for rubella, and if the woman is seronegative, vaccination is recommended after delivery.

As mentioned, varicella infection in pregnancy can cause severe maternal pneumonia in 5% to 10% of cases. Because of this, varicella zoster immune globulin (VZIG) should be given to all nonimmune pregnant women within 72 hours of exposure to varicella. Serologic testing should be done before VZIG is given because as many as 90% of women are immune. The effect of VZIG administration on fetal infection is unknown. Fetal disease—limb hypoplasia, cicatricial skin lesions, retardation, or cortical atrophy—occurs in less than 2% of fetuses. Maternal infection less than five days before delivery also causes neonatal infection due to the lack of time for the development of maternal protective IgG antibodies.

Parvovirus infection in pregnancy is one of the few treatable fetal conditions. The diagnosis in a pregnant woman is most commonly made after the discovery of nonimmune hydrops in her fetus. The diagnosis is confirmed either by maternal serologic testing or identification of the virus in amniotic fluid specimens by polymerase chain reaction (PCR). Parvovirus can cause bone marrow failure in the fetus, with fetal death occurring in as many as 5% of maternal infections. The hydrops resulting from this aplastic crisis has been successfully treated with the intrauterine transfusion of erythrocytes. In some cases, hydrops has resolved spontaneously. The current recommendation is for serial ultrasonograms to be done for as long as 16 weeks following maternal disease to monitor for the development of hydrops.

Cytomegalovirus is the most common cause of congenital viral infection. An estimated 0.2% to 2.2% of neonates are infected in utero, with 5% to 10% being symptomatic at birth. Fetal infection can occur with both primary and recurrent maternal infection; the likelihood of severe infection is much higher with primary infection, and early infection is associated with much more severe disease. Overall, fetal infection occurs in about 40% of cases of primary maternal infection. Although only 10% of infected infants are symptomatic at birth, symptoms, most commonly sensorineural hearing loss, will develop in an additional 5% to 10% by 2 years of age. Fetal infection in utero can be diagnosed by the culture of cytomegalovirus in the amniotic fluid or by PCR of amniotic fluid. The sensitivity of these two approaches is currently unclear.

Perhaps the virus with the greatest public health policy implication is the human immunodeficiency virus (HIV). The Centers for Disease Control and Prevention has reported that as of 1991, about 7,000 infants would be born each year to HIV-infected mothers and, of these, 1,000 to 2,000 would be infected. Because of this, a trial was begun in 1991 of maternal zidovudine therapy during pregnancy to prevent vertical transmission. Preliminary analysis of data from this trial has indicated a 67.5% reduction in the risk of HIV transmission. These results have led to the controversial recommendation that all women be screened for HIV during pregnancy and treated with zidovudine if infected.

What does the future hold for the diagnosis and management of viral diseases during pregnancy? An important advance will be the application of PCR-based diagnoses in fetuses. In this way, we will be able to more accurately identify affected fetuses. Also, new antiviral agents, if found safe for fetuses, may help decrease vertical disease transmission rates or actually treat fetuses in utero.

JAMES D. GOLDBERG, MD
San Francisco, California

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Assisted Reproductive Technologies

According to the most recent statistics published by the American Society for Reproductive Medicine, a total of 39,390 cycles of assisted reproductive technologies were initiated in the United States during 1994. A total of 9,573 deliveries occurred as a result of these technologies. Because of these high success rates, assisted reproductive technologies are increasingly being offered to infertile couples with a variety of diagnoses. Nevertheless, the most appropriate candidates for these technologies are those in whom other, more conventional treatments have failed. Patients with unexplained infertility are usually offered several cycles of superovulation and intrauterine insemination before proceeding to assisted reproductive technologies. Patients with pelvic factor infertility are appropriate candidates for in vitro fertilization (IVF), either after a failed tuboplasty or, if tubal disease is severe, in place of a pelvic reconstructive operation. Hydrosalpinges, however, should be either removed or opened by a cuff neosalpingostomy to drain the hydrosalpinx before IVF. Couples whose infertility is due to a male factor—for example, the husband's sperm have decreased fertilizing potential—are also appropriate candidates for IVF and, if the semen analysis is markedly abnormal, may benefit from micromanipulation of the gametes

To enhance success, most assisted reproductive programs use controlled ovarian hyperstimulation before the collection of gametes. The most commonly used regimen includes pretreatment with a gonadotropin-releasing hormone agonist and subsequent stimulation with human menopausal gonadotropins (hMG). The recombinant form of follicle-stimulating hormone will be introduced in the United States in 1997, and its use will most likely replace that of hMG in the same way that recombinant insulin has replaced other preparations. Natural-cycle (or "unstimulated") IVF, which depends on the selection of a single dominant follicle by the patient's own reproductive axis, continues to occupy a small niche within the assisted reproductive technologies. Whereas unstimulated cycles are easier to do, cheaper, and spare the endometrium the adverse effects of controlled ovarian hyperstimulation, the success rate of natural-cycle IVF is consistently lower than that of stimulated cycles. It appears that two cycles of natural-cycle IVF are required to achieve the success of a single stimulated cycle.

A key element of the assisted reproductive technologies is the collection of the oocytes. The transvaginal ultrasound-directed follicle-aspiration method is now standard. It can be achieved outside of an operating room with conscious sedation. The gamete intrafallopian transfer (GIFT) procedure, which involves placing gametes into the fallopian tubes, still requires general anesthesia and an operating room for the laparoscopy. As microlaparoscopic techniques become more commonplace, conscious sedation may also be used for the GIFT procedure.

Oocyte donation, a logical consequence of oocyte collection, has also grown substantially. This is due to the unanticipated finding that oocyte quality is a major determining factor of the success of the assisted reproductive technologies. Therefore, women with reduced oocyte quality, diminished ovarian reserve, and those older than 40 benefit substantially from the donation of oocytes from younger women. According to the most recent statistics, 3,119 donor oocyte cycles were initiated in the United States during 1994 with an overall success of 46.8% deliveries per retrieval. The technique of oocyte donation presents a unique physiologic configuration, as the oocytes are retrieved from one woman and are donated to another woman. Therefore, both ovarian stimulation and endometrial preparation can be controlled independently. For this reason, success rates of oocyte donation are consistently the highest of all the assisted reproductive technologies. No decline in success rates has been observed with increasing age of the recipient. Therefore, it appears that whereas the ovary ages, uterine receptivity does not decline, even for recipients well into their sixth decade of life. Regardless of the source of oocytes, the trophoblast and fetus are always immunologically distinct from the mother. Therefore, oocyte donation presents no additional difficulties with "rejection."

Whether or not success rates of the assisted reproductive technologies have already been maximized is not yet clear. Each year still seems to bring higher success rates on an individual clinic basis, as well as the overall statistics for the country as a whole. An additional benefit of these technologies is that success rates do not appear to decline over successive cycles. Therefore, they can be repeated for as many as three to six cycles to achieve high cumulative pregnancy rates. In most cases, the limiting step in the overall success of these procedures is the cost. The cost per cycle ranges from about $6,000 to $15,000, depending on the clinic, the type of technology (laparoscopy adds substantial cost), other interventions (intracytoplasmic sperm injection or embro freezing), and the amount of gonadotropins required to achieve stimulation. Whereas many states have mandated the coverage of assisted reproductive technologies, most insurance companies in California still do not cover this service. The national trend, however, is toward increased coverage of infertility treatment, including a certain number of cycles (usually 3) of treatment. Therefore, the future of these technologies appears headed toward technologic advancement, increased cost-effectiveness, and greater availability.

RICHARD J. PAULSON, MD
Los Angeles, California

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Mountain View

Alerts, Notices, and Case Reports

Ruptured Sinus of Valsalva Aneurysm in a Patient With Autosomal Dominant Polycystic Kidney Disease

ROBERT F. SPRUNG, MD
RENZO M. CATALDO, MD
MARTIN C. GREGORY, MD
MELINDA L. MARKS, MD
DAVID A. BULL, MD
SHELDON E. LITWIN, MD
Salt Lake City, Utah

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY disease is known to be associated with multiple structural flaws such as renal cysts, cerebral and aortic aneurysms, annuloaortic ectasia, and valvular insufficiency states.

Herein we describe the case of a patient with autosomal dominant polycystic kidney disease in whom a ruptured sinus of Valsalva aneurysm (SVA) was diagnosed through the use of echocardiography. This is the first documented account of an SVA defect in patients with this disease. The presence of this SVA may represent yet another structural defect in a condition known to be associated with multiple structural flaws that may have the unifying cause of a flawed gene product.

Report of a Case

The patient, a 54-year-old man with chronic renal failure due to autosomal dominant polycystic kidney disease who had been undergoing continuous ambulatory peritoneal dialysis for four months, was referred to the cardiology department of the University of Utah Medical Center after a new heart murmur was noted. The patient did not have chest pain, orthopnea, or dyspnea with exertion but did have two episodes of paroxysmal nocturnal dyspnea in the week before the referral.

The patient was diagnosed with autosomal dominant polycystic kidney disease at age 37. His medical history includes chronic hypertension, multiple urinary tract infections, anemia, hematochezia (thought to be due to diverticulosis), and a right inguinal hernia repair a month before referral. Medications were diltiazem hydrochloride, enalapril maleate, calcium carbonate, iron, vitamins, and epoetin alfa.

(Sprung RF, Cataldo RM, Gregory MC, Marks ML, Bull DA, Litwin SE: Ruptured sinus of Valsalva aneurysm in a patient with autosomal dominant polycystic kidney disease. West J Med 1996; 165:379–382)

From the Divisions of Cardiology (Drs Sprung, Cataldo, Marks, and Litwin), General Internal Medicine and Nephrology (Dr Gregory), and Cardiothoracic Surgery (Dr Bull), University of Utah Medical Center, and the Veterans Affairs Medical Center (Dr Sprung), Salt Lake City.

This work was done during the tenure of a Clinical Scientist Award from the American Heart Association to Dr Litwin.

Reprint requests to Sheldon E. Litwin, MD, Division of Cardiology, University of Utah Medical Center, 50 N Medical Dr, Salt Lake City, UT 84132.

On physical examination, the patient's blood pressure was 140/80 mm of mercury with a regular pulse rhythm and a rate of 83 beats per minute. His respiratory rate was 9 per minute, and he was afebrile. The carotid pulse was hyperdynamic with a prominent dicrotic notch. The jugular venous pressure was estimated to be normal. The lung fields were clear to auscultation. There was a palpable left parasternal thrill, with a forceful but nondisplaced apical impulse. A continuous mechanical murmur (grade 4/6) heard across the precordium was loudest at the left lower sternal border. The first and second heart sounds were normal. There were no extra heart sounds. On abdominal examination, the patient had no inflammation or tenderness at the Tenckhoff catheter exit site. The kidneys were palpable but not tender. A 12-lead electrocardiogram was normal.

A transthoracic echocardiogram (TTE) showed mild left atrial and left ventricular enlargement, moderate tricuspid regurgitation, and normal global left ventricular systolic function. Color Doppler imaging revealed a turbulent jet of blood flowing from the aortic root and terminating in the right atrium.

A transesophageal echocardiogram (TEE) using a multiplane 5-MHz probe showed hyperdynamic right ventricular function. The tricuspid leaflets appeared thickened, and there was moderate tricuspid regurgitation. A discrete jet of continuous turbulent flow was seen emanating from the right sinus of Valsalva and terminating in the right atrium (Figure 1). The abnormal flow was confined to a tubular structure measuring about 4 mm in internal diameter (Figure 2). Based on these images, the differential diagnosis included a right coronary artery to right atrial fistula (possibly due to rupture of a coronary artery aneurysm) versus a ruptured sinus of Valsalva aneurysm. Tricuspid valve endocarditis was also considered as a complicating feature.

Right and left heart catheterizations were done. Oximetric recordings showed an oxygen saturation increase of 8% between the right atrium and right ventricle. Hemodynamic measurements revealed right ventricular systolic and end-diastolic pressures to be 44 and 12 mm of mercury, respectively. The pulmonary artery wedge and left ventricular end-diastolic pressures were 18 and 14 mm of mercury, respectively. The calculated pulmonary to systemic flow ratio was 1.4. Angiography showed normal left ventricular wall motion and normal coronary arteries with a nondominant right coronary artery. These findings were consistent with mild biventricular volume overload produced by left to right intracardiac shunting. Aortic root angiocardiograms demonstrated a communication between the right sinus of Valsalva and the right heart (Figure 3). Aortic insufficiency was absent.

Surgical repair of the defect using a synthetic patch was undertaken. Intraoperative inspection confirmed the TEE findings of a ruptured SVA producing a 4-mm broad-based tapering tubular tract between the right sinus of Valsalva and the right atrium. This windsock deformity was

ABBREVIATIONS USED IN TEXT
SVA = sinus of Valsalva aneurysm
TEE = transesophageal echocardiogram
TTE = transthoracic echocardiogram

excised, and culture of the tissue grew *Enterobacter agglomerans*. Blood cultures from admission showed no growth. The patient received a six-week course of intravenous gentamicin sulfate and ceftriaxone sodium. His postoperative course was otherwise unremarkable. A TTE performed six weeks after discharge showed no recurrence of the fistula and resolution of the preoperative tricuspid regurgitation, but mild aortic valve regurgitation and mild left ventricular systolic dysfunction were seen. The patient remains clinically and hemodynamically stable and is being assessed for possible renal transplantation.

Discussion

Three defective genes located on chromosomes 4 and 16 are described as the putative cause of autosomal dominant polycystic kidney disease. The gene defect mapped to chromosome 16p13.3 accounts for 85% of cases of the disease. The resulting defective extracellular protein has been named "polycystin."[1] Autosomal dominant polycystic kidney disease has been associated with manifestations such as kidney and liver cysts; colon diverticula (in 80%); hernias (in 25%); cardiac valve (tricuspid, mitral, aortic) regurgitation; mitral and tricuspid valve prolapse; annuloaortic ectasia; and intracranial, aortic, and coro-

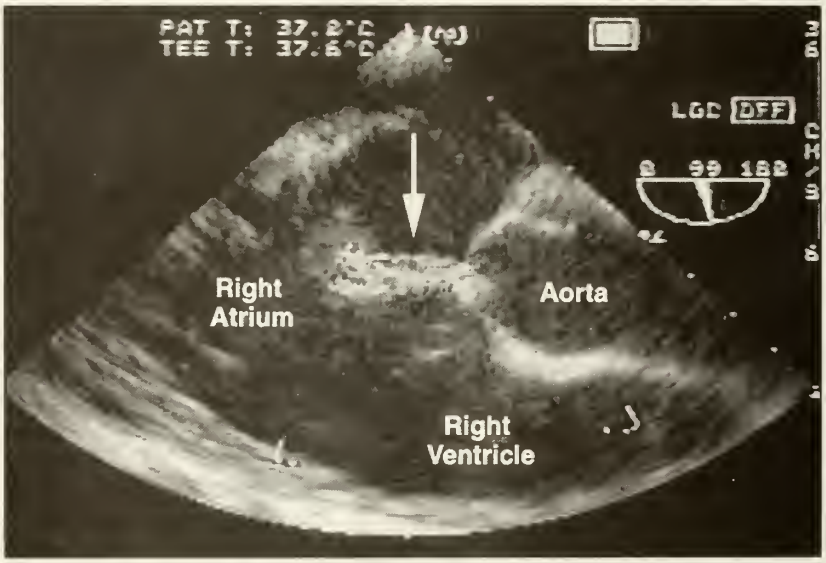

Figure 1.—A transesophageal echocardiogram shows continuous flow from the right sinus of Valsalva to the right atrium (arrow).

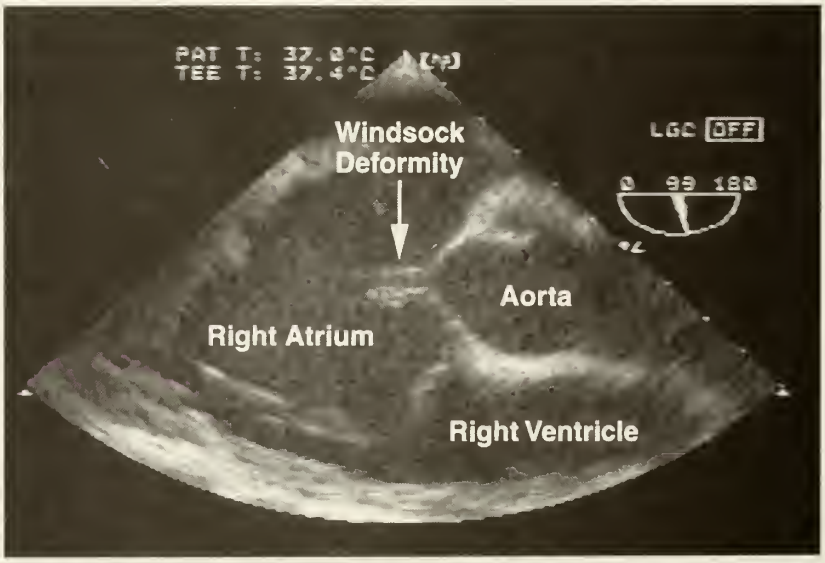

Figure 2.—A transesophageal echocardiogram shows the 4-mm diameter windsock-shaped structure (arrow) that confined the abnormal flow seen in Figure 1.

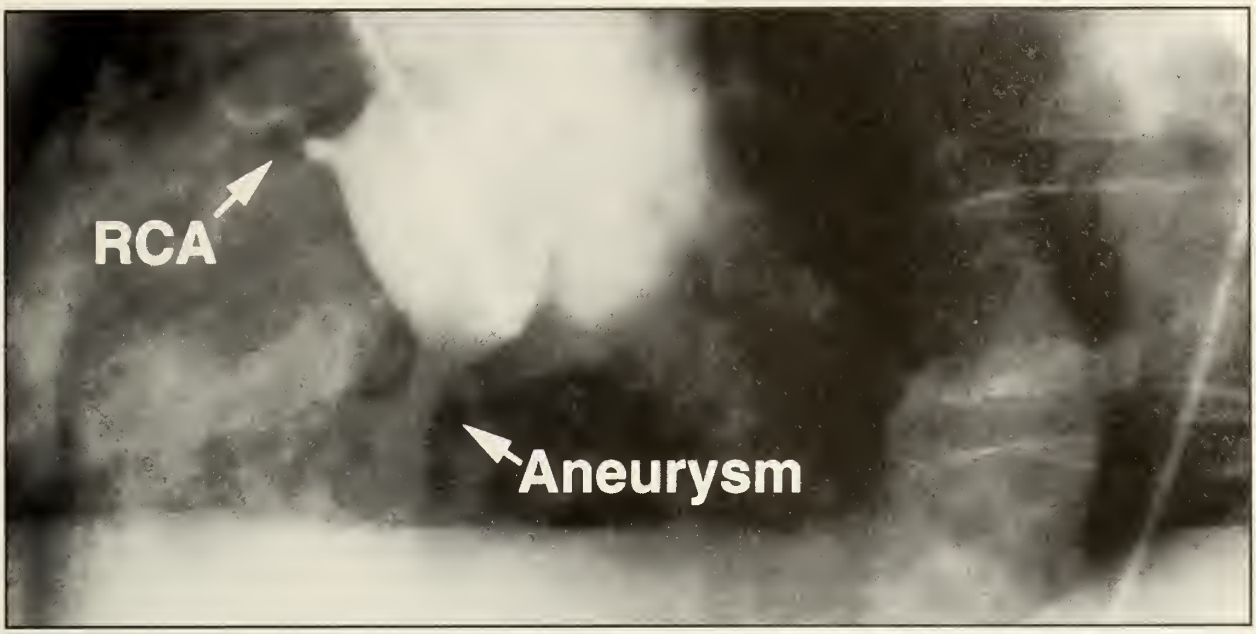

Figure 3.—An aortic root angiocardiogram shows the normally sited and sized nondominant right coronary artery **(RCA; arrow)** and the ruptured sinus of Valsalva aneurysm with a fistula to the right side of the heart **(arrow)**.

nary arterial aneurysms.[2] There is a lesser relationship between autosomal dominant polycystic kidney disease and cysts of the ovaries, seminal vesicles, epididymides, thyroid, and spleen. Electron-microscopic and biochemical data suggest that cystic structures are composed of and elaborate abnormal extracellular matrix proteins.[3] The structural integrity of the aortic valve cusps is dependent on the bond between their endothelial cell membranes and the trigonum fibrosum (type 1 and 3 collagen). This connection is composed of the basal lamina, the lamina densa portion of which contains an integral bond to collagen type 7 whose C terminal connects to the cardiac skeleton by type 4 collagen-anchoring plaques. Polycystin may direct the characteristics of the bond between type 4 collagen-anchoring fibrils and the proteoglycans of the lamina densa.[4] Therefore, if this bond or composition of the basal lamina is flawed—a possible defect in autosomal dominant polycystic kidney disease—the result would be a gross structural defect: loss of continuity between the aortic valve leaflet endothelium and the cardiac skeleton. Polycystin is not a component of collagen, but does have multiple extracellular domains and is a component of the lamina lucida of the basal lamina.[1] Therefore, the association between autosomal dominant polycystic kidney disease and acquired SVAs may be the production of sinus of Valsalva tissue with atypical composition that after repeated stress becomes fibrotic and dilates. Thus, these aneurysms are not true aneurysms. Rather, their walls are composed of avulsed fibrous tissue.

Secondary types of SVAs occur following aortic root fibrosis due to bacterial, fungal, or mycobacterial endocarditis; syphilis; iatrogenic trauma (postoperative ventricular septal defect and valve repairs); degenerative states such as atherosclerosis; or conditions associated with altered extracellular matrix such as cystic medial necrosis,[5] Marfan's syndrome,[5] aortoannular ectasia, osteogenesis imperfecta, pregnancy, and Behçet's disease.[6]

Causes of fibrosis such as an embryonic failure of fusion between the aortopulmonary and interventricular septum lead to the congenital type of SVA, with an incidence of 0.1% to 3.5% of all congenital heart defects.[5] This last type usually ruptures between the second and third decades of life. There is a fourfold male predominance in the congenital disorder, with Asian populations at greater risk than western races.[5] Sinus of Valsalva aneurysms (predominantly the congenital type) are associated with other structural lesions of the heart such as ventral septal defects in 40%, aortic insufficiency in 55%, pulmonic stenosis in 8%, and membranous subaortic stenosis in 5%.[7] The majority (77%) of congenital SVAs arise from the right coronary sinus and rupture into the right ventricle.[7] The SVAs that originate in the noncoronary artery sinus (about 20% of the total), usually develop fistulae to the right atrium, and rare aneurysms of the left sinus of Valsalva are most often acquired type.[5,7] In keeping with the inductive role of aortic pressure, some ruptures are precipitated by isometric physical stress.[5]

Although this patient had some of the noncystic manifestations of autosomal polycystic kidney disease—that is, colonic diverticula and an inguinal hernia—he had no cardiac valvular lesions, which are seen in 26% of patients with polycystic kidney disease.[3] Based on the patient's older age and lack of previous valvular lesions, this case likely represents an acquired SVA of unclear cause. Infection of the abnormal tissue was possibly secondary to a transient bacteremia due to diverticulitis or following peritoneal dialysis. Infection of the aneurysm may have led to its rupture, but the lack of evidence for endocardi-

tis from clinical examination, echocardiogram, and ventriculography suggests that valvular endocarditis was not present before or at the time of admission for surgical treatment. For this reason and because the Gram's stain of the aneurysmal wall showed no organisms, it seems unlikely that aortic valve endocarditis was responsible for the aneurysm development.

Although angiography is still considered by some the gold standard for the diagnosis of an SVA, if coronary artery assessment is not required, this case and others suggest that TTE with or without a TEE with color flow mapping may be an adequate diagnostic test for planning the surgical procedure in both SVA and coronary artery aneurysm repair.[7,8] The use of continuous-wave and color flow Doppler imaging enhances the specificity. If further delineation of the shunt is required, peripheral venous administration of agitated saline solution can reveal a negative jet in a right-sided receiving chamber. The transthoracic windows for optimal viewing are the basilar parasternal long and short axes.[5] In a review of 62 patients, the accuracy of echocardiography and angiography to define the receiving chamber, the presence of aortic insufficiency, and subaortic stenosis shows that the sensitivity and specificity for each method is 100% relative to intraoperative inspection.[7] The weakness of echocardiography is its poor sensitivity to detect SVA-associated pulmonic stenosis and ventricular septal defects (50% and 70%, respectively); however, the angiographic detection of SVA-associated ventricular septal defect was only 50%.[7]

This is the first case in modern literature of a patient with autosomal dominant polycystic kidney disease in whom a ruptured SVA developed. The SVA formation may be an additional feature of autosomal dominant polycystic kidney disease related to renal and hepatic cysts and cerebral and aortic aneurysms by the unifying cause of a flawed gene product. In this case, the windsock deformity produced by the ruptured aneurysm mimicked a coronary artery fistula.

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Diabetic Neuropathic Cachexia

ASLAM GODIL, MD
DIANE BERRIMAN, MD
Loma Linda, California
STEVE KNAPIK, DO
MICHAEL NORMAN, DO
FOUZIA GODIL, MD
Victorville, California
ANTHONY F. FIREK, MD
Loma Linda, California

DIABETIC NEUROPATHIC CACHEXIA is a rare syndrome first described in 1974[1] and seen predominantly in patients in their sixth or seventh decade with mild non–insulin-dependent diabetes mellitus (NIDDM). It is characterized by substantial involuntary weight loss, anorexia, depression, severe autonomic dysfunction, and peripheral neuropathy that develop over a short period of time. Generally other specific end-organ complications of diabetes mellitus, like retinopathy or nephropathy, are absent. The cause remains unclear, and there are no known precipitating factors. Because of its highly variable and profound clinical presentation, this syndrome is often confused with neuropathic carcinomatosis or an occult cancer. The overall prognosis is good, and symptoms generally resolve spontaneously over one to two years.

In this age of constrained resources, it is important that this clinical syndrome be recognized and considered in patients with diabetes mellitus. Since the original report, about 25 cases have been reported in the English-language literature,[1–8] with only three cases in females.[3–5] Herein we report a case of diabetic neuropathic cachexia and review the literature.

Report of a Case

The patient, a 57-year-old man, was initially admitted to the Jerry L. Pettis Veterans Affairs Medical Center (Loma Linda, California) in December 1992 with a diagnosis of the new onset of NIDDM. His chief symptom at that time was an accelerated unintentional weight loss of 18 kg (40 lb) over six months. The patient had numbness and severe burning over the soles of his feet, progressing proximally to involve his legs, anterior abdomen, and midthoracic area, developing rapidly over the same period. He also had polyuria, polydipsia, blurring of vision, general weakness, fatigue, decreased appetite, early satiety, constipation, impotence, and depression with insomnia. He had no history of dysphagia, odynophagia, diarrhea, nausea, vomiting, or stool incontinence. He had

(Godil A, Berriman D, Knapik S, Norman M, Godil F, Firek AF: Diabetic neuropathic cachexia. West J Med 1996; 165:382–385)

From the Division of Gastroenterology and Nutrition (Dr A. Godil), General Internal Medicine (Dr Berriman) and Endocrinology (Dr Firek), Jerry L. Pettis Veterans Affairs Medical Center and Loma Linda University and School of Medicine, Loma Linda; and Department of Internal Medicine, Desert Valley Medical Group (Drs Knapik, Norman, and F. Godil), Victorville, California.

Reprint requests to Aslam Godil, MD, Division of Gastroenterology and Nutrition, Rm 1562, Loma Linda University Medical Center, 11234 Anderson St, Loma Linda, CA 92354.

TABLE 1.—*Classification of Diabetic Polyneuropathy**

Type of Neuropathy	*Description*
Generalized polyneuropathy	
Distal symmetric polyneuropathy	Predominantly sensory, chronic onset, gradually ascends over months to years; often affects large and small fibers; decreased position, vibration, pain, and temperature sensation with decreased or absent stretch reflexes
Acute painful diabetic neuropathy (diabetic neuropathic cachexia)	Acute onset, painful distal neuropathy, rapidly ascends over weeks to months, associated with substantial weight loss, depression, and autonomic dysfunction; often reversible
Autonomic polyneuropathy	Often associated with distal symmetric polyneuropathy; features include orthostatic hypotension, resting tachycardia, gastroparesis, diarrhea or constipation, impotence, neurogenic bladder
Subclinical polyneuropathy	Early mild form of distal symmetric polyneuropathy, often detected by abnormal electrophysiologic studies
Multiple mononeuropathies	
Proximal lower extremity motor neuropathy (diabetic amyotrophy)	Acute onset, in patients with long-standing diabetes; asymmetric proximal lower extremity weakness accompanied by back, hip, and thigh pain with preserved sensations
Truncal neuropathy	Acute or gradual onset of unilateral pain in the chest or abdomen with hyperpathic sensation and muscle weakness involving thoracic roots (T-3 to T-12); often seen with long-standing diabetes
Mononeuropathy	
Cranial mononeuropathy	Involves oculomotor, abducent, trochlear, and facial nerves in descending order of frequency
Compression mononeuropathy	Median nerve in carpal tunnel syndrome; ulnar nerve and peroneal nerve

*From Ross.[21]

no relevant history of alcohol and tobacco use.

On presentation, the patient's blood pressure was 144/96 mm of mercury, supine, with a pulse rate of 89 beats per minute and 135/92 mm of mercury, standing, with a pulse rate of 93 beats per minute. He weighed 59 kg (131 lb) with a height of 178 cm (70 in). He was pale and appeared chronically ill and depressed, with a general loss of subcutaneous tissue. Muscle wasting was noted, more in the lower than the upper extremities. Vibration sensation, deep tendon reflexes, and muscle strength were decreased in the lower extremities. The results of the physical examination were otherwise unremarkable.

A random serum glucose level was 40.0 mmol per liter (721 mg per dl), and a complete blood count, urinalysis, and routine chemistry values were normal. The patient was admitted to the hospital, given intravenous fluids, and treatment with an oral hypoglycemic agent—glyburide, 5 mg a day—was started. His serum glucose levels remained adequately controlled, with a follow-up glycosylated hemoglobin level of 0.069 (6.9%).

In February 1993, the patient was readmitted because of syncope, continued weight loss (now weighing 56 kg [124 lb]), and progressive paresthesias, impotence, weakness, and fatigue that limited his walking to only a few steps. On examination he was markedly orthostatic, with a blood pressure of 124/82 mm of mercury, supine, with a pulse rate of 107 beats per minute and 62/44 mm of mercury, standing, with a pulse rate of 110 beats per minute. He appeared more cachectic and chronically ill, with pronounced flattening of his affect. There was no evidence of retinopathy. The extremities showed profound symmetrical and diffuse wasting, with associated bilateral weakness in both proximal and distal muscle groups, more pronounced in the lower than the upper extremities. Reflexes were symmetrically decreased in both upper and lower extremities with absent ankle jerks. Sensory examination showed dysesthesias in his feet, legs, and hands extending up to the midanterior chest, diminished proprio- ception and vibration sense, and numbness of the feet and hands to light touch and pinprick, suggesting involvement of both large and small fibers. The patient's gait was unsteady due to muscle weakness and paresthesias, and he had to use a cane. He was given support stockings with partial improvement in orthostatics. In March 1993, the patient was seen in the outpatient clinic and had continued weight loss (now 54 kg [120 lb]). His serum glucose levels remained under good control (range, 5.4 to 8.9 mmol per liter [98 to 160 mg per dl] at home) with a glycosylated hemoglobin level of 0.07. A regimen of low-dose amitriptyline hydrochloride at bedtime was started for his paresthesias.

The patient underwent an extensive workup that included chest x-ray, thyroid-stimulating hormone, thyroxine, triiodothyronine, vitamin B_{12} and folate levels, a rapid plasma reagin test, creatine kinase level, serum cortisol level, thyroid scan, magnetic resonance imaging of the thoracic spine, ultrasonogram of the liver, gallbladder, and pancreas, quantitative stool fat, colonoscopy, and esophagogastroduodenoscopy with a small bowel biopsy, all of which were normal. Electromyography and nerve conduction studies showed reduced amplitude of motor and sensory nerve action potentials and mild slowing of nerve conduction velocities, consistent with axonal injury.

Since his discharge, he has been observed in the medical clinic for about three years. In June 1993, the patient weighed 56 kg (123 lb) (a 1.4-kg [3-lb] weight gain), and since then he has gained 16 kg (35 lb), no longer has postural hypotension, and his paresthesias are greatly improved. He is able to walk with minimal difficulty. His depression and impotence have resolved, and he is main-

tained on a regimen of glyburide, 5 mg per day, and amitriptyline, 25 mg per day at bedtime.

Discussion

The cause of diabetic neuropathic cachexia remains unclear. From reported cases, no precipitating factors such as exposure to toxins or chemicals have been identified.[1–8] Nerve and muscle biopsies in these patients have shown neurogenic atrophy in the muscle[1] and pronounced involvement of both large and small fibers with axonal degeneration, no inflammatory cells or amyloid deposits, and normal vasa nervorum.[1,7] This suggests that the neuropathy of diabetic neuropathic cachexia is not a microvascular disease process as usually seen in classic diabetic neuropathy. This theoretically could explain the reversibility of this process, although strong evidence is lacking.

Electromyography and nerve conduction studies reveal a reduced amplitude of motor and sensory action potentials and a mild reduction in conduction velocities, indicating peripheral polyneuropathy from axonal degeneration. Weight loss is attributed to anorexia due to depression and pain.[1] There have been four cases of diabetic neuropathic cachexia and weight loss caused by malabsorption[4] due to exocrine pancreatic insufficiency, with normal endoscopic retrograde cholangiopancreatography, although a correlation of pancreatic insufficiency with this syndrome is lacking. Depression is attributed to neuropathic pain, and as neuropathy clears, depression and anorexia resolve simultaneously. Impotence is not a consistent feature of this syndrome. It is thought to be due to inanition, depression, and possibly neuropathy. Because potency returns in most patients, a psychogenic basis or inanition would be a more likely cause.[1]

Diabetic neuropathic cachexia is seen predominantly in men in their sixth or seventh decade with NIDDM, usually a mild form, often well controlled with diet or an oral hypoglycemic agent.[1] The classic presenting features are weight loss, peripheral neuropathy, autonomic neuropathy, and emotional changes. Rare cases have been reported in patients who are young,[7] have insulin-dependent diabetes mellitus,[7] and are female.[3–5] Usually NIDDM and diabetic neuropathic cachexia are diagnosed simultaneously. Occasionally patients may have NIDDM for several years before this syndrome develops.[5,6,8]

The hallmark of this syndrome is the extreme rarity of specific associated microangiopathic end-organ complications of diabetes, such as retinopathy or nephropathy, despite profound neurologic involvement. Notable weight loss of as much as 60% of the total body weight is a consistent feature in these patients. Weight loss occurs rapidly, usually over a period of three to six months, and it is generally not related to the control of the diabetes mellitus. Weight loss in classic diabetic neuropathy is not unusual,[9] but it is rare to have a weight loss of this magnitude.

The neuropathy of diabetic neuropathic cachexia is distinct from various other diabetic neuropathies (summarized in Table 1). Usually it is severe, peripheral, bilaterally symmetrical,[6] occurs in close association with the onset of diabetes mellitus, and involves both sensory and motor components. Sensory symptoms may be a pure sensory loss, paresthesias, aching, burning, or shooting pain, and dysesthesias, all usually worse at night.[1] They usually begin distally in the lower extremities and rapidly ascend over weeks to months to more proximal levels, as compared with months to years in classic diabetic neuropathy,[10] and may eventually involve the upper extremities, chest, and abdomen.[8] Motor manifestations include general wasting with weakness.[1] Patients appear emaciated with decreased muscle strength, more pronounced in the proximal lower extremities than in the upper extremities.[1] There has been a case of diabetic neuropathic cachexia progressing to a flaccid paralysis of the lower extremities and bowel incontinence.[5] Deep tendon reflexes are usually symmetrically decreased, often with an absence of ankle reflexes.[1,3,5,6] Position and vibratory sense is also decreased or absent.[1,5,6]

The most interesting feature of neuropathy is a spontaneous resolution of severe pain and other neuropathic symptoms within two years.[1–8] There are a few cases in which mild paresthesias may persist.[1,7] The average duration of neuropathy ranges from 12 to 48 months. Autonomic neuropathy is much less common than peripheral neuropathy in these patients. The effects of autonomic dysfunction include impotence, orthostatic hypotension, and, rarely, constipation.[1,4,7,8]

A case of neurogenic bladder confirmed by cystometrogram has been reported that presented as an abdominal mass and obstructive renal failure,[3] with the eventual return of normal bladder function after diabetic neuropathic cachexia resolved. There is no doubt that autonomic involvement in these patients is underestimated because of the focus on the manifested sensory neuropathic complaints. The neuropathy of diabetic neuropathic cachexia should be differentiated from diabetic amyotrophy,[11] which is typically seen in patients with long-standing diabetes mellitus, characterized by substantial weight loss and the acute or subacute onset of moderate to pronounced asymmetric wasting and weakness of the pelvifemoral muscles. This weakness is accompanied by back, hip, and thigh pain with preserved sensation in the regions of pain. The site of lesion appears to involve either lumbosacral roots or plexus. The prognosis is fair to good with good functional recovery.

Depression is universally associated with this syndrome.[1–8] Frequent crying episodes, insomnia, anxiety, and irritability are the characteristic features. The painful peripheral neuropathy may be the primary cause for depression, as all these patients had no history of depression, and their depression resolved with resolution of the neuropathy. Most are able to resume normal activities, including employment, without a noted recurrence of depression.

The presentation of diabetic neuropathic cachexia in middle-aged to elderly men as profound weight loss and severe neuropathic pain would direct a physician to evaluate for an occult malignant tumor. Carcinomatous neuropathy has a prevalence of 2% to 3%[12] and is predominantly

associated with cancers of the lungs, pancreas, stomach, ovaries, breasts, and lymphoma and leukemias. These patients usually have mixed peripheral neuropathy, often associated with ataxia.

The workup for diabetic neuropathic cachexia should be individually based. It is a diagnosis of exclusion, and because the symptoms in this syndrome generally occur rapidly in middle-aged or elderly patients, suggesting malignancy, the workup should be systemic, which can be both extensive and resource-intensive. A progressive "negative" evaluation in a patient with such a dramatic presentation often leads to the use of more esoteric and expensive technologies. In this age of constrained resources, it is important that this clinical syndrome be recognized and considered in patients with diabetes mellitus.

Treatment is primarily supportive and symptomatic. With the release of the Diabetes Control and Complications Trial results,[13] there is evidence that the tight control of glucose levels in insulin-dependent diabetes mellitus delays the onset and slows the progression of diabetic neuropathy and other end-organ complications.[14] The role of intensive therapy in patients with NIDDM is not clear. In diabetic neuropathic cachexia, a condition where there is no evidence of microvascular end-organ damage[1,7] and that often presents early in the course of diabetes mellitus, the role of aggressive therapy is not clear. There have been cases in which tight glucose control with oral hypoglycemic agents and sometimes insulin produced some lessening of the neuropathic symptoms. The only evidence in favor of this is that there is an intracellular accumulation of sorbitol and a depletion of myoinositol in hyperglycemic states that abate with the control of serum glucose levels.[15] Some patients with diabetes with classic peripheral neuropathy have benefited from continuous insulin infusion.[16]

Antidepressants are of great help in the symptomatic management of the neuropathy and depression associated with this syndrome. A case of diabetic neuropathic cachexia was reported in which a regimen of fluphenazine dihydrochloride and amitriptyline hydrochloride decreased the neuropathic pain within 24 hours after therapy was initiated, and the pain continued to resolve subsequently.[6] Our patient was given amitriptyline, but the improvement of neuropathy was gradual, more consistent with the natural course of the disease. The use of agents like phenytoin, carbamazepine, and clonazepam has inconsistently lessened symptoms in classic diabetic neuropathy. They are worth a therapeutic trial, although their specific role in resolving symptoms in this syndrome is uncertain. Good nutritional support with a high-protein and -carbohydrate diet may be of considerable help because anorexia is the main factor leading to weight loss.

Strong reassurance to patients, optimistic views about the course of the disease, and close follow-up are important in managing these patients. The prognosis is good. The most intriguing feature of diabetic neuropathic cachexia is the propensity of symptoms to spontaneously resolve over one to two years. With the resolution of pain and lifting of the depression, anorexia abates, leading to weight gain in most cases, often to the original weight. Furthermore, patients regain the ability to walk and regain continence and potency. In some patients, mild paresthesias persist. Most patients resume their normal lifestyle, with most maintaining good diabetes control with diet alone or with a low-dose oral hypoglycemic agent. Follow-up for longer than five years has shown no relapse of this symptom complex.

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Topics in Primary Care Medicine

Approach to Patients With Hirsutism

ROLAND SAKIYAMA, MD, *Los Angeles, California*

Hirsutism is a common medical condition that in most women is due to the polycystic ovary syndrome or is idiopathic. For a few women, hirsutism signals a serious underlying disorder such as an ovarian or adrenal tumor, congenital adrenal hyperplasia, or Cushing's syndrome. A detailed medical history and examination can identify women in whom a serious disease is suspected and for whom laboratory evaluation is warranted. Measurements of serum testosterone, dehydroepiandrosterone, and 17α-hydroxyprogesterone levels, and 24-hour urinary cortisol concentrations are important screening tests. Therapy is directed at suppressing ovarian or adrenal androgen production, inhibiting the conversion of testosterone to dihydrotestosterone, or antagonizing the effects of androgens at the receptor level.

(Sakiyama R: Approach to patients with hirsutism. West J Med 1996; 165:386–391)

Hirsutism is a common clinical condition affecting about 5% of women in the United States.[1] All too often, physicians dismiss hirsutism as a concern that does not deserve their clinical acumen. Perhaps this response is due to a lack of knowledge of the proper evaluation and management of hirsutism or the notion that hirsutism is merely a cosmetic problem. For most women, hirsutism is not a manifestation of a serious disorder, but rather a possible source of emotional disability. For some women, hirsutism is a warning sign of a more serious underlying problem. Appropriate management can be determined after a carefully directed history, physical examination, and limited laboratory testing.*

Hirsutism is defined as the excessive growth of androgen-responsive terminal hair in women. Therefore, for most women, hirsutism is a cutaneous manifestation of androgen excess. True hirsutism must be distinguished from hypertrichosis—that is, excessive growth of vellus or non–androgen-responsive hair. Vellus is fine, downy hair that is usually unpigmented. Terminal hairs are dark, thick, and found in the sex hormone–responsive areas of the pubis, axilla, back, face, chest, and abdomen. Androgens promote an increase in the number and thickness of terminal hairs in these areas. Women with androgen-dependent hirsutism either have exposure to excessive androgens or manifest a heightened androgen-receptor sensitivity to normal circulating levels of androgen. For other women, hirsutism is a non–androgen-dependent abnormality—that is, an adverse effect to certain drugs or a genetic characteristic, such as in women of Mediterranean or East Indian origin.

Testosterone and dihydrotestosterone are true androgens as defined by their ability to interact with the androgen receptor. Testosterone binds to cell receptors, enters the cell cytoplasm, and is converted to dihydrotestosterone by a 5α-reductase enzyme. Dihydrotestosterone, in turn, is bound to specific cytoplasmic receptors. Potential androgens are dependent on a conversion to testosterone and include dehydroepiandrosterone (DHEA) and androstenedione. Dehydroepiandrosterone is the major adrenal androgen that can be converted to testosterone, or sulfated to DHEAS before secretion. Measuring the DHEAS level is the preferred plasma test of adrenal androgen production because DHEA shows a circadian and menstrual rhythm not found with DHEAS. Androstenedione is the major C19 steroid produced by the ovaries, although the ovaries are also able to secrete testosterone and dihydrotestosterone. In normal women, two thirds of plasma testosterone is derived from the adrenal cortex through peripheral formation from DHEA and androstenedione.

Causes of Hirsutism

Causes of hirsutism can be classified as ovarian, adrenal, drug-related, idiopathic, or genetic (Table 1).[2] Ovarian disorders include the polycystic ovary syndrome and ovarian tumors. Adrenal disorders include congenital adrenal hyperplasia, Cushing's syndrome, and adrenal tumors. Hirsutism may also occur with the ingestion of anabolic steroids or as an adverse effect of a limited group of medications (see Table 1). Idiopathic hirsutism is defined by normal androgen concentrations and a lack of any identifiable underlying disorder. It has been proposed that idiopathic hirsutism results from an increased androgen-receptor sensitivity to normal androgen levels. More than 95% of women with hirsutism are found to have either idiopathic hirsutism or the polycys-

*See also the editorial by S. J. Agarwal, MB,BS, and H. L. Judd, MD, "What We See Most, We Understand Least," on pages 392–393 of this issue.

From the Division of Family Medicine, University of California, Los Angeles (UCLA), School of Medicine.
Reprint requests to Roland Sakiyama, MD, Division of Family Medicine, UCLA School of Medicine, 200 UCLA Medicine Plaza, Ste 220, Los Angeles, CA 90095-1628.

ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone, corticotropin
CT = computed tomography
DHEA = dehydroepiandrosterone
DHEAS = sulfated form of DHEA
FDA = Food and Drug Administration
FSH = follicle-stimulating hormone
GnRH = gonadotropin-releasing hormone
LH = luteinizing hormone
MRI = magnetic resonance imaging
SHBG = sex hormone–binding globulin

tic ovary syndrome.[3]

The polycystic ovary syndrome is the most common identifiable cause of androgen hypersecretion in women. The underlying defect in this syndrome is postulated to be a nontumorous dysfunction of luteinizing hormone (LH) hypersecretion, with a subsequent stimulation of thecal and stromal ovarian cells to produce androgens. The polycystic ovary syndrome encompasses a wide spectrum of clinical manifestations. Patients may present with classic "polycystic ovary disease"—obesity, hirsutism, anovulation, and enlarged multicystic ovaries. On the opposite end of the spectrum, women with mild polycystic ovarian syndrome may not be obese and have regular ovulatory cycles and normal ovaries, with only subtle hormonal aberrations and hirsutism. Luteinizing hormone levels are frequently elevated in the polycystic ovary syndrome, but often to such a modest degree that its absolute value remains within the normal reference range. If the ratio of LH to follicle-stimulating hormone (FSH) is measured, however, it is frequently increased to 2.5 or greater in women with the polycystic ovary syndrome (most normal ovulatory women have an LH:FSH ratio of 1.0). Total plasma testosterone levels are elevated in 40% to 60% of women with this syndrome. In the other women, levels of total testosterone are normal, but those of free testosterone are elevated. Free testosterone represents the nonprotein-bound hormone that is thought to most closely reflect cellular hormonal actions. The major binding protein for testosterone is sex hormone–binding globulin (SHBG), which is decreased in women with the polycystic ovary syndrome and accounts for elevated levels of free testosterone despite normal total testosterone levels.

Ovarian and adrenal tumors are uncommon causes of hirsutism. Adrenal carcinomas are typically large by the time they produce excessive androgens. Adrenal adenomas can produce androgens and are typically small and difficult to localize. Ovarian tumors include Sertoli-Leydig cell tumors, hilar cell tumors, lipoid cell tumors, and adrenal rest tumors. Elevations in DHEAS levels suggest an adrenal origin of androgen production, whereas greatly elevated testosterone concentrations signal a possible ovarian or adrenal tumors.[3]

Cushing's syndrome is caused by the chronic overproduction of glucocorticoids and, to a lesser extent, adrenal androgens. Skin findings due to excessive androgen production include hirsutism, acne, and temporal hair recession, in addition to glucocorticoid-associated

TABLE 1.—*Causes of Hirsutism**

General	*Specific Cause*
Ovarian	Polycystic ovary syndrome
	Neoplasms
	Sertoli-Leydig cell tumors
	Hilar cell tumors
	Lipoid cell tumors
	Adrenal rest tumors
Adrenal	Congenital adrenal hyperplasia
	21-Hydroxylase deficiency
	11β-Hydroxylase deficiency
	3β-Hydroxysteroid dehydrogenase deficiency
	Cushing's syndrome
	Neoplasms
	Adrenal carcinoma
	Adrenal adenoma
Drugs (proprietary name)	Cyclosporine (Sandimmune)
	Danazol (Danocrine)
	Phenytoin (Dilantin)
	Glucocorticoids
	Minoxidil (Loniten)
	Diazoxide (Hyperstat)
	Anabolic steroids
Idiopathic	
Genetic	

*From Carr.[2]

findings of thin skin and purple striae. Classic congenital adrenal hyperplasia presents in infancy and is due to a deficiency of 21-hydroxylase, 11β-hydroxylase, or 3β-hydroxysteroid dehydrogenase adrenal enzymes. An attenuated or nonclassic form of congenital adrenal hyperplasia may present in adolescence or young adulthood.[4,5] A partial deficiency of the 21-hydroxylase enzyme is the most common form of nonclassic congenital adrenal hyperplasia. Decreased 21-hydroxylase activity leads to increased concentrations of 17α-hydroxyprogesterone, which in turn is converted to testosterone.

Idiopathic hirsutism is found in 50% of women evaluated for hirsutism. Idiopathic hirsutism is defined by normal physical and laboratory findings in women with the onset of excessive hair growth in puberty or young adulthood. They do not have signs of virilization and manifest a slow progression of their hirsutism. Increased sensitivity of the hair follicles to normal circulating androgens is thought to cause the hirsute state.

History and Physical Examination

The primary goal of the history and physical examination is to identify patients in whom hirsutism is the cutaneous manifestation of a serious underlying disease. Hirsutism due to the polycystic ovary syndrome or idiopathic causes typically begin between the ages of 15 and 25 years and progresses slowly. Symptoms starting later in life, coupled with a rapid progression, suggest a more serious underlying disorder, such as an ovarian or adrenal tumor or Cushing's syndrome. The exception is peri-

menopausal women who may have more hair growth in their perimenopausal years due to an increased production of adrenal androgens. Women with greater elevations in androgen levels have virilizing symptoms such as balding, deepening of the voice, increased libido, or decreased body fat. Virilization is not typical of idiopathic hirsutism or the polycystic ovary syndrome and suggests a more serious disorder. Women should be carefully questioned about symptoms associated with specific underlying diseases. For example, those with the polycystic ovary syndrome may have amenorrhea, oligomenorrhea, infertility, or obesity. A recent weight gain with a cushingoid body habitus and hypertension suggests Cushing's syndrome, whereas flank pain or a mass coupled with weight loss may be due to an adrenal cancer. Finally, the use of prescribed medications or anabolic steroids should be carefully reviewed.

The examination is directed at documenting the extent and distribution of terminal hair and uncovering any clues as to an underlying cause. Hirsutism can be quantitated by the use of the Ferriman and Gallwey score.[6] The extent of hirsutism is evaluated in nine body areas—upper lip, chin, chest, upper arms, upper abdomen, lower abdomen, thighs, and upper and lower back—and each area is given a point score of 0 (no hirsutism) to 4 (overtly virile). A total score of 8 or higher is consistent with the diagnosis of hirsutism. Physical findings of virilization include receded temporal hair, increased laryngeal size, decreased body fat, atrophied breasts, masculine musculature, and clitoromegaly (a clitoris of greater than 1.0 cm in diameter). Patients with Cushing's syndrome may have acne, purple striae, or centripetal obesity. A bimanual pelvic examination is done to exclude an ovarian mass, which is found in about half of women with ovarian tumors, or enlarged ovaries (polycystic ovary syndrome).

Laboratory Evaluation

In women who are presumed to have the polycystic ovary syndrome or idiopathic hirsutism, only a limited laboratory evaluation is required. For women with suspicious historical or physical findings, a more extensive laboratory evaluation is done to exclude androgen-secreting adrenal or ovarian tumors, Cushing's syndrome, or the nonclassic form of congenital adrenal hyperplasia. The two most important screening tests are measurements of total serum testosterone and DHEAS levels. Testosterone levels of greater than 7 nmol per liter (2.0 ng per ml) suggest the presence of an androgen-secreting ovarian or adrenal tumor, and DHEAS levels of greater than 19 μmol per liter (700 μg per dl) suggest an adrenal tumor.[7] Elevations of testosterone and DHEAS levels to this degree are not specific for a neoplastic cause, as they can also be found in 50% of women with benign disorders. Testosterone and DHEAS levels below these thresholds, however, essentially exclude an androgen-secreting tumor. For women with abnormally elevated testosterone levels and normal DHEAS levels, a search for an ovarian tumor is begun with ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) of the pelvis. If both testosterone and DHEAS levels are abnormally elevated, then a radiologic evaluation of the adrenal glands is performed with MRI or CT.

To exclude the possibility of Cushing's syndrome, a 24-hour urine specimen is collected and submitted for free cortisol determination. A urine free cortisol concentration of greater than 275 nmol per day (100 μg per 24 hours) is considered abnormal. Alternatively, the patient may be given an overnight dexamethasone suppression test in which 1 mg of dexamethasone (2 mg for obese women) is given orally at 11 PM, with a serum cortisol level measured at 8 AM the next morning. Normally, dexamethasone will suppress cortisol values to less than 140 nmol per liter (5 μg per dl). Women having a nonsuppressed serum cortisol level or abnormal urinary free cortisol concentrations are referred for complete endocrinologic evaluation. To evaluate for 21-hydroxylase–deficient nonclassic congenital adrenal hyperplasia, a morning plasma 17α-hydroxyprogesterone level is measured. A 17α-hydroxyprogesterone level of 6.0 nmol per liter (2.0 ng per ml) or lower rules out this adrenal gland deficiency.[5] A women with a 17α-hydroxyprogesterone level above 6.0 nmol per liter should be referred for adrenocorticotropic hormone (ACTH; corticotropin)–stimulated testing.

The diagnosis of the polycystic ovary syndrome can be confirmed with laboratory determinations of serum testosterone, DHEAS, LH, and FSH levels. In the polycystic ovarian syndrome, the total testosterone level is modestly elevated in 40% to 60% of patients. In women found to have normal testosterone levels, the levels of free testosterone will usually be elevated. The DHEAS level is normal or occasionally slightly elevated, and the LH:FSH ratio is usually greater than 2.5. Pelvic ultrasonography is not required unless an ovarian mass is found on pelvic examination; however, in obese women in whom the pelvic examination is difficult, an ultrasonogram may be helpful. Enlarged polycystic ovaries are found infrequently and usually in women who manifest other features of the polycystic ovary syndrome, such as obesity, oligomenorrhea, or amenorrhea.

Treatment

Mechanical methods of hair removal are an effective adjunct for the control of hirsutism and may be the most appropriate therapy for women with limited areas of unwanted hair growth. For women with widespread hirsutism, combining medical therapy with shaving, plucking, waxing, or electrolysis can result in a more rapid response. In addition, women who have previously abandoned these physical methods may wish to resume these measures after medical therapy has slowed the rate of new hair growth. The most common adverse effects are skin irritation (bleaching, chemical depilatories), pitting or scarring (electrolysis), or folliculitis (plucking, waxing). Shaving is considered the safest method of temporary hair removal and, contrary to popular belief,

once hair is shaved, it does not return in a darker or thicker state.

For women found to have an ovarian or adrenal tumor, Cushing's syndrome, or 21-hydroxylase–deficient nonclassic congenital adrenal hyperplasia, appropriate referral should be made for specific therapy. Most women's hirsutism will be caused by the polycystic ovary syndrome or idiopathic causes, and medical therapy can be offered. Treatment is more effective at preventing further hair growth than reversing long-established hirsutism, and therefore, women with the recent onset of hirsutism are more likely to respond to treatment than those with long-standing hirsutism. In addition, because hair growth is inherently a slow process, patients are advised that an observable response may not be evident in the first three to six months. Finally, determining a therapeutic response is often difficult. Although the Ferriman-Gallwey score is useful, it is often cumbersome and hampered by the concomitant use of mechanical methods of hair removal. A patient's subjective evaluation of her hair growth may be the only measure of successful therapy, with often the most useful measure of success being a reduction in the time a woman spends removing unwanted hair.

Medical therapy for hirsutism may be directed at several levels (Table 2). Drugs can suppress ovarian or adrenal androgen secretion or block the action of androgens in target hair follicles. If a hormone abnormality has been determined, then therapy is directed at reversing that abnormality. For example, a woman with an elevated testosterone level is given drugs that suppress ovarian androgen production. Women with normal testosterone concentrations are presumed to have an increased end-organ sensitivity to androgens and therefore are more likely to respond to drugs that antagonize the tissue effects of androgens.

TABLE 2.—*Medical Management of Hirsutism*

Diagnosis	*Medication (Proprietary Name)*
Ovarian androgen suppression	Oral contraceptives
	GnRH agonist
	Depot leuprolide (Lupron Depot)
	Nafarelin acetate (Synarel)
	Cyproterone acetate* (Androcur, Diane)
Adrenal androgen suppression	Glucocorticoids
5α-Reductase inhibitors†	Finasteride (Proscar)
Antiandrogens	Spironolactone (Aldactone)
	Cyproterone acetate* (Androcur, Diane)

GnRH = gonadotropin-releasing hormone

*Not available in the United States.
†Inhibition of testosterone to dihydrotestosterone.

Suppressing Ovarian Androgen Production

Oral contraceptives are the most commonly used method to suppress ovarian androgen production. Progestins inhibit gonadotropin secretion, thereby reducing ovarian-stimulated androgen secretion. The estrogen component stimulates the hepatic synthesis of SHBG, which binds circulating testosterone, and lowers the amount of free testosterone available to hair follicles. This is especially helpful in women with the polycystic ovary syndrome who often have lower SHBG levels.

When prescribing oral contraceptives, clinicians must be aware of the possible androgenic activity of the progestational component. 19-Nortestosterone derivatives, such as norgestrel, norethindrone, levonorgestrel, and to a lesser extent, ethynodiol diacetate and lynestrenol, show partial androgen activity, especially at higher doses.[8] The dose of these progestins should be kept to a minimum. The use of a combination of ethinyl estradiol (35 μg) and ethynodiol diacetate (1 mg) found in Demulen 1/35 has often been recommended for this reason. Newer progestins, such as desogestrel, gestogen, and norgestimate, have no important androgenic activity and should be advantageous in treating hirsute women. Oral contraceptives combining low-dose estrogen and these nonandrogenic progestins include Desogen, Ortho-Cept, Ortho-Cyclen, and Ortho Tri-Cyclen. Although these oral contraceptives offer a theoretic advantage, comparisons of different oral contraceptives with regards to their effects on hirsutism are lacking.

The response to oral contraceptive use varies, but it is more likely to occur in women with elevated testosterone levels. The efficacy of oral contraceptive use for the treatment of hirsutism has recently been questioned.[9] It may be that a few hirsute women will have substantial improvement with oral contraceptive treatment alone. Until further studies are available, oral contraceptives continue to be a first-line treatment for the majority of women with hirsutism. These hormones have the added benefits of regulating menses and ensuring contraception in women taking antiandrogens.

Gonadotropin-releasing hormone (GnRH) agonists used long term can suppress ovarian androgen production in hirsute women. The long-term use of these agonists alone, however, often leads to hypoestrogenic side effects such as hot flashes, osteoporosis, and urogenital atrophy. Therefore, they are combined with oral contraceptives or conjugated estrogens and progestins in the treatment of hirsutism.[10,11] The GnRH agonists used in the treatment of hirsutism include nafarelin acetate as an intranasal spray given 400 μg twice a day, or depot leuprolide acetate, 3.75 mg monthly. The use of GnRH agonists for the treatment of hirsutism is severely limited by cost, and therefore therapy with GnRH agonists should be reserved for moderate to severe hirsutism that is unresponsive to oral contraceptive alone or combined with antiandrogens.

Adrenal Androgen Suppression

Glucocorticoids are used to suppress ACTH-stimulated adrenal androgen production and therefore are useful for patients with the nonclassic form of congenital adrenal hyperplasia. Treatment may be initiated with dexamethasone, 0.25 to 0.5 mg; prednisone, 2.5 to 5.0

mg; or hydrocortisone, 10 to 20 mg. Glucocorticoids are administered in the evening or at bedtime to suppress the nightly ACTH surge.

5α-Reductase Inhibitors

Finasteride is the only 5α-reductase inhibitor available in the United States. Finasteride blocks the conversion of testosterone to dihydrotestosterone, thereby inhibiting the androgen effects on the hair follicle. Finasteride has been approved by the Food and Drug Administration (FDA) for the treatment of benign prostatic hypertrophy, but not for hirsutism. Studies have compared the use of finasteride with that of spironolactone (an antiandrogen) and found them to have equal effectiveness in the treatment of hirsutism.[12] The use of both finasteride and spironolactone decreased terminal hair diameters by 14% and improved the Ferriman-Gallwey scores by 11%. Finasteride use is well tolerated, but studies of animals have reported ambiguous genitalia in male offspring of treated females, and therefore finasteride should not be used during pregnancy and should be combined with a reliable method of contraception, such as oral contraceptives.

Antiandrogens

One of the most useful group of medications for the treatment of hirsutism are the antiandrogens. These drugs competitively inhibit the binding of testosterone and dihydrotestosterone to their respective receptors. The most commonly used antiandrogen is spironolactone, which is an aldosterone antagonist commonly used as a potassium-sparing diuretic. Spironolactone has the additional property of competitively binding to dihydrotestosterone receptors, thus limiting the response of tissues to endogenous androgens. Although not approved by the FDA for the treatment of hirsutism, several studies have shown it to be an effective drug for this indication.[13,14] Therapy is started with a dosage of 50 mg twice a day, which is then increased to 100 mg twice a day if no response is seen after three months. Half to three quarters of women will have a noticeable improvement with spironolactone. Adverse effects are more common at higher doses and include irregular menses (25%), gastrointestinal cramping, diarrhea, nausea, lethargy, and headache. Hyperkalemia may occur, especially in elderly women, in women with diabetes mellitus, or if taken with other drugs that may increase serum potassium levels (angiotensin-converting enzyme inhibitors). Therefore, periodic monitoring of serum potassium levels is recommended. Spironolactone should not be used in pregnancy, and appropriate contraception must be recommended. Combinations of oral contraceptives and spironolactone are, therefore, commonly prescribed for the treatment of hirsutism, to ensure contraception, and to regulate the menses.

Flutamide is a potent, nonsteroidal, selective antiandrogen without progestational or estrogenic activity that has been effective in the treatment of hirsutism.[9] Flutamide is given at a dosage of 250 mg twice a day combined with an estrogen-containing oral contraceptive. Adverse effects include dry skin and increased appetite. A major concern with flutamide is a potentially fatal drug-induced hepatitis that occurs in 0.5% of patients given this drug. Flutamide use can also cause ambiguous genitalia in male offspring, and therefore, contraception must be maintained. Its use is not recommended for the routine treatment of hirsutism due to its expense and possible toxic side effects.

Cyproterone acetate has properties of both a potent progestin and a moderately potent antiandrogen. Cyproterone acetate, therefore, acts at two levels in the pathophysiologic process of hirsutism. It competitively inhibits the binding of dihydrotestosterone to its cytoplasmic receptor and also inhibits gonadotropin secre-

TABLE 3.—*Guidelines for the Treatment of Hirsutism*

Diagnosis	*Initial Therapy, Dosage**	*Alternative Therapy, Dosage**
Polycystic ovary syndrome	Oral contraceptives (Demulen 1/35, Desogen, Ortho-Cept, Ortho-Cyclen, or Ortho Tri-Cyclen) Spironolactone (Aldactone), 50 to 100 mg bid	Finasteride (Proscar), 5 mg qd GnRH agonist (Lupron Depot), 3.75 mg monthly
Idiopathic	Oral contraceptives (Demulen 1/35, Desogen, Ortho-Cept, Ortho-Cyclen, or Ortho Tri-Cyclen) Spironolactone (Aldactone), 50 to 100 mg bid	Finasteride (Proscar), 5 mg qd GnRH agonist (Lupron Depot), 3.75 mg monthly
Nonclassic congenital adrenal hyperplasia	Glucocorticoids: prednisone, 5 mg qhs; or dexamethasone, 0.25 mg qhs	
Cushing's syndrome	Surgical excision of ACTH-secreting pituitary adenoma or ectopic ACTH-secreting tumor; adrenalectomy for adrenal hyperplasia	
Adrenal tumor	Surgical excision	
Ovarian tumor	Surgical excision	
Drug-induced	Discontinue medication	

ACTH = adrenocorticotropic hormone, bid = twice a day, GnRH = gonadotropin-releasing hormone, qd = daily, qhs = every night at bedtime

*Proprietary names are given in parentheses. Demulen 1/35-21 (GD Searle & Co) contains ethynodiol diacetate, 1 mg, and ethinyl estradiol, 35 μg. Desogen (Organon Inc) contains desogestrel, 0.15 mg, and ethinyl estradiol, 0.03 mg. Ortho-Cept 21 (Ortho Pharmaceutical Corp) contains desogestrel, 0.15 mg, and ethinyl estradiol, 0.03 mg. Ortho-Cyclen 21 (Ortho Pharmaceutical Corp) contains norgestimate, 0.25 mg, and ethinyl estradiol, 0.035 mg. Ortho-Tricyclen (Ortho Pharmaceutical Corp) contains norgestimate, 0.18 mg, and ethinyl estradiol, 0.035 mg. Lupron Depot (TAP Pharmaceuticals) contains 3.75 mg of leuprolide acetate.

tion because of its progestational properties.[15,16] An oral contraceptive using cyproterone acetate as the progestin would appear to be well suited for the treatment of hirsutism. Cyproterone acetate is not available in the United States in any form, but it is available as a single agent (Androcur) or combined with estrogen in an oral contraceptive (35 or 50 μg of ethinyl estradiol and 2 mg of cyproterone acetate) in Europe, Canada, and Mexico (see Table 2). Drug-induced hepatitis is a rare complication that may require periodic monitoring of liver enzyme levels.

Treatment Guidelines

Initial therapy for women with hirsutism due to the polycystic ovary syndrome or idiopathic causes can be started with spironolactone or oral contraceptives (Table 3). Certainly, in women with menstrual irregularities or contraceptive concerns, oral contraceptives are considered a first-line agent. Spironolactone is generally well tolerated and usually efficacious. Women who are intolerant or nonresponsive to spironolactone use may be given a trial of finasteride combined with an estrogen-containing oral contraceptive. In women with severe hirsutism who are not responsive to the use of antiandrogens, oral contraceptives, and finasteride, the use of GnRH agonists should be considered. Finally, if hirsutism continues or worsens despite these treatment modalities, the clinician should consider reevaluating for a serious underlying disorder.

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Editorials

What We See Most, We Understand Least

HIRSUTISM CAN BE DEFINED as the presence of excessive terminal hair in a woman in areas typically associated with male sexual hair growth. It is a sensitive marker for increased androgen action and can be found in combination with other clinical features of hyperandrogenism including acne and male pattern hair loss. The Ferriman and Gallwey score is the conventional and most widely used method to objectively document the degree of hirsutism.[1] We recommend that it be used whenever assessing a patient with hirsutism. Before deciding if a woman has hirsutism, her ethnic origin should be taken into consideration. It should be remembered that a genetic predisposition to the development of terminal hair (because of inherited differences in 5α-reductase activity) varies with ethnic origin. Clearly, what may be considered hirsutism for a Scandinavian woman may well be within the normal limits for a woman from the Middle East or the Mediterranean region.

Androgens are cholesterol-derived C19 steroids that are principally secreted from the ovaries and adrenal cortex. In addition, small amounts may be produced through conversion from other steroids in tissues such as the liver, muscle, and fat. Under normal circumstances, testosterone is the major biologically active circulating androgen, and the vast majority of it in the circulation is bound to sex hormone–binding globulin (SHBG). Because only the free component of a steroid hormone is functionally active, the level of SHBG and, to a lesser degree albumin, can have a profound influence on the activity of testosterone and other androgens. For example, a small decrease in SHBG in the presence of a constant concentration of total testosterone, as found in obesity, can produce a state of clinical hyperandrogenism. Conversely, through hepatic effects, estrogens can increase SHBG and hence lead to a decrease in free testosterone levels. This can be used clinically to treat symptomatic hyperandrogenism.

Due to 5α-reductase activity at the level of the hair follicle, testosterone, androstenedione, and to a lesser extent, other unbound circulating androgens are converted to dihydrotestosterone, a highly potent androgen. This then acts by androgen receptors on the pilosebaceous unit to promote terminal hair growth. Areas of the body that have high levels of 5α-reductase activity are particularly sensitive to the effects of androgens. These normally include the pubic and axillary regions. In the presence of high androgen levels or increased 5α-reductase activity, however, terminal hair growth in other, typically male, areas may ensue. These include the face, chest, lower abdomen, upper thighs, and back. The development of hirsutism, therefore, is dependent not only on the concentrations of free C19 steroids, but also on the degree of 5α-reductase activity and the presence of functioning androgen receptors.

Despite being the most common endocrinopathy of women during the reproductive years, the polycystic ovary syndrome is also the least understood cause of hirsutism. Stein and Leventhal were the first to describe the syndrome of hirsutism, amenorrhea, and obesity in association with sclerocystic ovaries.[2] Since this initial description in 1935, there has been much debate regarding virtually every feature of this syndrome. Even the fundamental aspects, such as its precise definition, are disputed. In reality, it is probable that the polycystic ovary syndrome represents a heterogeneous spectrum of disorders rather than a single disease.

The definition of the polycystic ovary syndrome most prevalent in North America is a clinical one that relies on evidence of chronic anovulation with hyperandrogenism. Although this may be associated with mild elevations in serum prolactin, dehydroepiandrosterone-sulfate (DHEAS), and testosterone concentrations, specific pituitary, adrenal, and ovarian conditions should be excluded before making the diagnosis. It is often helpful to think of the polycystic ovary syndrome as a diagnosis of exclusion, and it should be noted that the appearance of polycystic ovaries is not required. When using this definition, estimates of its prevalence range from 5% to 10%.

The health consequences of the polycystic ovary syndrome are varied and are thought to largely result from either the excess production of luteinizing hormone, androgens, insulin, or unopposed noncycling estrogens. Women with this syndrome may present with a number of complaints including hirsutism, infertility, obesity, irregular bleeding, amenorrhea, recurrent pregnancy loss, acne, and hair loss.

Most women with the polycystic ovary syndrome have an element of insulin resistance. The degree of this resistance is only partly related to the body mass index because even nonobese women with this syndrome can be affected. The resultant hyperinsulinemia has two important effects: there is increased stimulation of ovarian theca cell androgen production by both insulin and insulinlike growth factor receptors, and there is a lowering of SHBG levels. Indeed, the correlation between SHBG levels and the degree of insulin resistance is pronounced. The consequence of these two insulin-mediated effects is to increase the availability of bioactive androgen.

Occasionally women with the polycystic ovary syndrome have mild elevations of adrenal androgen (DHEAS) levels. It can be postulated that in these cases, DHEAS can be used as substrate in the ovary for the production of more potent androgens.

Unopposed estrogenic stimulation of the endometrium can result in endometrial hyperplasia or cancer. Cases of endometrial cancer have been reported in women as young as 17 years and typically occur in obese persons. Furthermore, it has been reported that as many as a quarter of patients with endometrial carcinoma younger than 40 years have the polycystic ovary syndrome. Fortunately, the tumors are invariably well-differentiated adenocarci-

nomas, and because of this, they are usually at an early stage at diagnosis. It is postulated that unopposed estrogen also leads to hyperprolactinemia in about 25% and galactorrhea in 13% of women with the polycystic ovary syndrome.

Other long-term health consequences of the polycystic ovary syndrome include a markedly increased risk for cardiovascular disease, with an estimated 11-fold increased risk of myocardial infarction between the ages of 50 and 61 years. Recent preliminary reports also suggest an increased risk of breast cancer in women with this syndrome.

Because the cause of this common syndrome is unknown, it is not surprising that there is no specific treatment for it. It is clear that because of the many serious health problems attributable to the polycystic ovary syndrome, the management of a patient with this condition requires attention not just to the immediate complaints, but also to the prevention of long-term sequelae. Patient education is of paramount importance if long-term compliance is to be achieved.

In Europe, the antiandrogen cyproterone acetate is one of the most commonly employed treatments of hirsutism associated with the polycystic ovary syndrome. It has progestogenic activity and is combined with ethinyl estradiol in a combined oral contraceptive (Diane). In North America, cyproterone acetate is unavailable, and spironolactone, a mineralocorticoid antagonist with androgen receptor-blocking activity, is used extensively. Flutamide, another antiandrogen, and finasteride, a specific 5α-reductase inhibitor, have been reported to have good effect in the treatment of hirsutism associated with the polycystic ovary syndrome. For the optimal efficacy of spironolactone and flutamide treatments, these drugs are often prescribed with a combined oral contraceptive pill. If oligomenorrhea or amenorrhea is present, the addition of an oral contraceptive pill will also eliminate the increased risk of endometrial cancer. Maximal effects with any of the above forms of therapy take in excess of four months to manifest clinically. Hence, it should be recommended that patients wait at least this long to allow the cessation of new terminal hair growth before undergoing physical forms of hair removal to remove any pretreatment unwanted hair.

Correcting obesity can further augment the therapeutic results. In one long-term noncontrolled prospective study of obese women with the polycystic ovary syndrome, a 5% reduction in body weight led to a decrease in serum insulin and free testosterone levels and a rise in SHBG levels.[3] This group was also substantially more likely to have improvement in reproductive function, as documented by more regular menstrual cycles and improved pregnancy rates, than those women who lost less than 5% of their baseline weight.

The differential diagnosis of hirsutism includes a number of other conditions. Unless the physician specifically explores the possibility of each of these, the correct diagnosis will not be made. For example, treating a woman with the complaints of hirsutism, obesity, and menstrual irregularity with oral contraceptives because of the presumed diagnosis of the polycystic ovary syndrome would not be appropriate if she has the Cushing's syndrome. In this issue of the journal, Roland Sakiyama, MD, presents an overview of the approach to patients with hirsutism.[4] The possible causes, necessary diagnostic evaluation, and treatments are covered in a systematic manner. It is fortunate that most causes of hirsutism are relatively benign. Steroid-secreting tumors are uncommon, even in a reproductive endocrinology clinic setting.

SANJAY K. AGARWAL, MB,BS
Interim Director, Reproductive Medicine
Department of Obstetrics and Gynecology
Cedars-Sinai Medical Center
Ste 160W, Cedars-Sinai Medical Center
8700 Beverly Blvd, Los Angeles, CA 90048

Assistant Professor
Department of Obstetrics and Gynecology
UCLA School of Medicine

HOWARD L. JUDD, MD
Professor and Vice Chair
Department of Obstetrics and Gynecology
UCLA School of Medicine

Chair, Department of Obstetrics and Gynecology
Olive View/UCLA Medical Center
Los Angeles and Sylmar, California

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The Search for Viable Myocardium

LEFT VENTRICULAR FUNCTION is among the most important determinants of long-term prognosis in patients with coronary artery disease.[1] It is now apparent that left ventricular dysfunction does not always represent an irreversible process, as was once thought, but may be reversible, at least in part, in a large subset of patients with coronary artery disease. Left ventricular performance may be reduced on the basis of regionally ischemic, stunned, or hibernating myocardium rather than fibrosis from previous myocardial infarction. The detection of reversibly dysfunctional myocardium is clinically relevant because regional and global left ventricular function in such patients may improve substantially after revascularization. A third or more of patients with chronic coronary artery disease and left ventricular dysfunction manifest a substantial improvement, and even a return to normal, of ventricular function after bypass surgery or angioplasty.[2] This improvement in systolic function, in turn, translates into enhanced survival. Thus, as discussed in the review by Birnbaum and Kloner elsewhere in this issue of the *Journal*,[3] the recognition that many patients with coronary artery disease and left ventricular dysfunction may not have irreversibly damaged ventricles, and the development of cost-effective imaging techniques to

identify viable myocardium, have important clinical implications.

Stunning and Hibernation

Two distinct pathophysiologic processes, myocardial stunning and myocardial hibernation, have been proposed as the mechanisms for reversible contractile dysfunction in humans, and these complex processes have been described in detail and in an understandable manner in Birnbaum and Kloner's review.[3] Stunning represents contractile dysfunction after an episode of myocardial ischemia, resulting from ischemic injury with possible superimposed reperfusion injury.[4] Hibernation, on the other hand, does not represent an injury but is thought to be an adaptive, protective mechanism by which the myocardium inhibits its contractile elements in the setting of sustained reductions in blood flow to match its oxygen demands with the reduced oxygen supply.[5] It is important to note, however, that the distinct definitions of these terms, in black and white on the printed page, become indistinct margins with important shades of gray in many clinical situations. For example, acute left ventricular dysfunction after reperfusion therapy for myocardial infarction could represent myocardial stunning if the infarct-related artery is widely patent, but could also represent acute hibernation as an adaptive response to persistent hypoperfusion when the previously occluded infarct-related artery has been opened but a residual high-grade, flow-limiting stenosis remains.

Similarly, chronic left ventricular dysfunction that improves after revascularization is usually thought to represent myocardial hibernation, and the improvement in function is considered the result of improved blood flow under resting conditions.[5] In some situations, however, blood flow may be normal at rest in dysfunctional myocardium, and sustained contractile dysfunction results from repeated episodes of reversible ischemia and repetitive postischemic stunning.[6] This situation will also improve only if revascularization or other interventions are performed to abolish the ischemic episodes. In this situation, revascularization does not improve blood flow at rest, as in the case of hibernation, but improves vasodilator reserve during stress, thereby reducing the extent and magnitude of reversible ischemia. This is one form of stunning in which myocardial dysfunction will not improve spontaneously, and so spontaneous improvement in function is not a prerequisite for stunning, as suggested by Birnbaum and Kloner.[3]

It is also likely that both hibernation and repetitive stunning may occur together in the same patient and perhaps even in the same myocardial region. A myocardial region that is hibernating at rest, with a critical balance of reduced perfusion and reduced function, may develop ischemia during exercise, followed by a process of postischemic stunning superimposed on the baseline hibernating state.[7]

Thus, the clinical distinction between hibernating myocardium, stunned myocardium, or a combination of these processes is difficult and often impossible. Luckily, this distinction is also of limited importance. Instead, the clinically important issue is the understanding that left ventricular dysfunction in many patients with coronary artery disease is not an irreversible process related to fibrosis but may represent a reversible process that will improve if recognized and if the patients are revascularized. Noninvasive methods have evolved during the past decade to assess myocardial viability and are ideally suited for this purpose. These include methods to study metabolic activity, membrane integrity, and inotropic reserve.[2,7,8]

Identifying Viable Myocardium

Positron emission tomography. Positron emission tomography (PET) has emerged as a promising method for demonstrating viable myocardium in patients with compromised left ventricular function. Myocardial viability is identified by PET on the basis of intact metabolic activity in regions of severely underperfused and dysfunctional myocardium. The most extensive experience thus far has been achieved using fludeoxyglucose F 18 (^{18}FDG) as a marker of regional exogenous glucose use in such hypoperfused regions. In particular, a pattern of enhanced ^{18}FDG uptake in regions with reduced perfusion (called the ^{18}FDG-blood flow "mismatch") indicates that viable tissue has preferentially shifted its metabolic substrate toward glucose rather than fatty acids or lactate.[8] The finding of preserved metabolic activity in myocardial regions with reduced blood flow has been demonstrated in a total of six studies, involving 146 patients, to be an accurate clinical marker with which to distinguish viable myocardium from myocardial fibrosis, with positive and negative predictive accuracies of 82% and 83%, respectively, for predicting which dysfunctional regions will manifest improved function after revascularization.[7] Thus, PET appears to yield excellent viability information.

Thallous chloride Tl 201 imaging. The requirements for cellular viability include intact sarcolemmal function to maintain electrochemical gradients across the cell membrane, as well as preserved metabolic activity to generate high-energy phosphates. These processes also require adequate myocardial blood flow to deliver substrates and wash out the metabolites of the metabolic processes. As the retention of thallium (thallous chloride Tl 201) with time is an active process that is a function of cell viability and cell membrane activity, as well as blood flow, thallium should in theory be taken up and retained by myocardial regions that also retain ^{18}FDG and other metabolic tracers.

The thallium protocols using single-photon emission computed tomography (SPECT), which have been best adapted for assessing myocardial viability, are as follows: thallium reinjection imaging, in which imaging is repeated after a small additional dose of thallium is administered at rest after a period of redistribution following stress imaging,[9] and thallium imaging without exercise using a rest-redistribution protocol.[10] It has been shown in 13 SPECT studies, totaling 378 patients, that these protocols each achieve a positive predictive accuracy of 69% and negative predictive accuracies of 89% and 92%, respectively.[7] In each of these protocols, both defect reversibility and severity of the thallium defect are

important markers of viable myocardium, and the positive predictive value can be enhanced considerably by performing a quantitative analysis of defect severity.

Technetium Tc 99m sestamibi imaging. Unlike thallium, technetium Tc 99m sestamibi does not redistribute appreciably after being administered during exercise or at rest. Thus, ^{99m}Tc-sestamibi may have inherent disadvantages relative to thallium for assessing viability. This concept is supported by studies showing that rest-exercise ^{99m}Tc-sestamibi imaging underestimates viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction compared with exercise-redistribution-reinjection thallium imaging.[11] Recent data suggest, however, that quantitative analyses of regional ^{99m}Tc-sestamibi activity after a resting injection of the tracer may increase the accuracy of sestamibi for identifying viable tissue.[10] Although these results are promising, this agent remains more of an investigational agent than a preferred agent for this purpose.

SPECT metabolic markers. The role of SPECT imaging using metabolic tracers has been less extensively studied compared with the large number of studies using thallium or ^{99m}Tc-sestamibi. Technetium-based or iodinated fatty acids have been studied in preliminary trials and appear promising.[12] In addition, the ability to image PET tracers, such as ^{18}FDG, using high-energy collimators, is a new and unique application of current SPECT technology that may allow a more routine use of PET metabolic tracers for assessing viability.[13] The accuracy of SPECT imaging of PET tracers for this purpose has not been extensively evaluated to date.

Dobutamine echocardiography. Previously ischemic, stunned myocardium maintains contractile reserve that can be identified following the administration of inotropic agents such as dopamine, isoproterenol, and dobutamine, as well as by postextrasystolic potentiation. Low-dose dobutamine infusion to enhance regional systolic wall thickening during echocardiography has recently been proposed as a clinical method to assess contractile reserve and has been applied successfully to patients after thrombolytic therapy for acute myocardial infarction and also to patients with chronic left ventricular dysfunction.[14] The results of 15 studies of chronic coronary artery disease, involving a total of 402 patients, indicate that this method predicts the recovery of left ventricular function after revascularization with a predictive accuracy virtually equivalent to that achieved using PET protocols, with positive and negative predictive accuracies of 83% and 81%, respectively.[7]

Clinical Implications

The identification of viable myocardium has become an area of intense interest for several reasons. Among these is the unique potential of nuclear cardiology techniques to distinguish viable regions on the basis of perfusion, cell membrane integrity, and metabolic activity and the ability of dobutamine echocardiography to assess regional inotropic reserve. Although the available data imply that each of these methods has similar diagnostic accuracy, larger scale studies comparing the use of PET, thallium, and dobutamine echocardiography are required in patients undergoing revascularization to determine the relative efficacies of these methods in identifying viable myocardium.

The evolving PET data indicate that the identification of viable myocardial tissue in patients with coronary artery disease and left ventricular dysfunction has several important, clinically relevant implications. First, the augmentation in regional systolic function after revascularization, as predicted by ^{18}FDG-blood flow mismatch, results in a substantial and predictable increase in the global left ventricular ejection fraction.[8] This increase in left ventricular ejection fraction after revascularization in patients with viable myocardium appears to translate into an improvement in the prognosis.[2,7,8,15] Finally, the improvement in left ventricular function after revascularization in patients with viable myocardium is also associated with a considerable lessening of symptoms of congestive heart failure.[15] These survival and function results have important implications in the management of patients with congestive heart failure because coronary artery disease accounts for as much as 80% of cases of heart failure in this country. Although more definitive data are required before full conclusions can be drawn, these data suggest that patients with impaired left ventricular function who have extensive evidence of underperfused but viable myocardium are a subgroup of patients who may have substantial improvement in outcome if identified and treated with myocardial revascularization. These patients appear to have the potential for improved left ventricular function, decreased symptoms, and improved survival. Whether these clinical outcome data derived from PET studies can be generalized to viability markers obtained from thallium imaging or dobutamine echocardiography awaits further study.

ROBERT O. BONOW, MD
Chief, Division of Cardiology
Northwestern University Medical School
250 East Superior St, Ste 524
Chicago, IL 60611

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Correspondence

Violence in America

To the Editor: Laurence D. Chu, MS, and Susan B. Sorenson, PhD, begin their study of homicide trends in California by stating that the United States leads industrialized nations with the highest homicide rate.[1] We frequently see similar claims in both scientific and lay publications, often accompanied by statements such as, "Violence is as American as apple pie." Table 1 lists the suicide and homicide rates for all 76 nations that release these data.[2] The figures are for the most recent available year.

In fact, 13 nations admit to higher homicide rates: Bahamas, Brazil, Colombia, Ecuador, El Salvador, Estonia, Kazakhstan, Kyrgyzstan, Mexico, Philippines, Puerto Rico, Russia, and Venezuela. Belarus, Latvia, Lithuania, and Ukraine come close. (Three nations including Russia have both higher suicide and higher homicide rates.) Violence is a serious problem: America clearly has too much. Nevertheless, the seriousness of a problem does not justify inaccurate statements.

DAVID C. STOLINSKY, MD
1200 State St, Rm 10-421
Los Angeles, CA 90033

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TABLE 1.—*Rates of Suicide and Homicide per 100,000 Population in 76 Nations*

Nation	Rates: Suicide	Rates: Homicide
Albania	1.4	3.9
Argentina	6.6	5.0
Armenia	2.6	5.7
Australia	12.0	1.6
Austria	22.3*	1.5
Bahamas	1.2	10.8*
Bahrain	3.1	0.4
Barbados	4.7	7.1
Belarus	20.3*	6.9
Belgium	19.3*	1.4
Brazil	3.2	20.2*
Bulgaria	16.9*	4.5
Canada	12.8*	2.2
Cape Verde	2.4	1.7
Chile	5.6	2.9
China	17.6*	1.4
Colombia	2.7	74.4*
Costa Rica	4.2	4.2
Czechoslovakia	17.1*	2.1
Denmark	22.0*	5.0
Dominican Republic	2.1	4.8
Ecuador	4.4	10.3*
Egypt	0.0	0.5
El Salvador	11.3	28.1*
Estonia	27.1*	11.0*
Finland	28.8*	3.4
France	20.2*	1.1
Germany	16.7*	1.2
Greece	3.7	1.4
Guatemala	0.5	3.3
Guyana	1.7	0.3
Hong Kong	13.0*	1.8
Hungary	38.7*	4.0
Iceland	10.7	1.1
Ireland	9.8	0.6
Israel	7.3	1.2
Italy	7.8	2.9
Japan	16.8*	0.6
Kazakhstan	19.1*	11.8*
Korea, South	7.1	1.4
Kuwait	0.9	0.5
Kyrgyzstan	12.4	13.9*
Latvia	26.0*	9.2
Lithuania	26.0*	7.5
Luxembourg	15.1*	2.1
Macao	8.1	1.9
Malta	5.0	1.7
Martinique	12.8*	4.3
Mauritius	13.9*	2.1
Mexico	2.4	17.2*
Netherlands	10.7	1.2
New Zealand	13.9*	1.9
Nicaragua	2.7	5.7
Norway	15.8*	1.5
Panama	3.0	5.2
Philippines	0.5	19.5*
Poland	14.9*	2.9
Portugal	8.8	1.5
Puerto Rico	10.0	22.6*
Romania	11.6	4.9
Russia	26.6*	15.3*
Sao Tome	0.9	2.8
Singapore	11.6	1.8
Slovenia	32.3*	2.5
Spain	7.5	1.0
Suriname	13.4*	3.6
Sweden	17.2*	1.3
Switzerland	20.8*	5.2
Trinidad	12.0	7.7
Ukraine	20.6*	8.0
United Kingdom	8.0	0.9
United States	12.4	9.8
Uruguay	10.3	4.4
Venezuala	4.8	12.1*
Yugoslavia	15.3*	2.0
Zimbabwe	7.5	6.9

*Figure exceeds US figures.

* * *

Drs Sorenson and Chu Respond

To the Editor: Dr Stolinsky does not challenge our research methods, findings, or conclusions. Instead, he challenges one statement—the third sentence of the article—that was properly cited as findings of Fingerhut and Kleinman of the National Center for Health Statistics as reported in *The Journal of the American Medical Association* (*JAMA*) in 1990.[1] Thus, it might be contended that Stolinsky's quarrel should be redirected to the 1990 *JAMA* article. Nonetheless, we are placed in a position to defend the integrity of the research we cited—an easy task.

We would like to reaffirm that the sentence and the *JAMA* article in question addressed homicide risk in industrialized nations. To that end, the introduction of international comparisons of suicide rates is not relevant. Second, whereas there is some disagreement regarding the definition of industrialized and developing nations, most would agree that the 13 countries listed by Stolinsky—Bahamas, El Salvador, Mexico, Philippines, and so forth—are not fully industrialized nations. Third, although there have been discussions about changing its status, Puerto Rico continues to be considered a United States territory, not an independent nation.

SUSAN B. SORENSON, PhD
Professor in Residence

LAWRENCE D. CHU, MS
Doctoral Student in Epidemiology

University of California, Los Angeles
School of Public Health
10833 Le Conte Ave
Los Angeles, CA 90095-1722

REFERENCE

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Do Premedical Students Fear Being Sued?

To the Editor: I commend John M. Chuck, MD, for addressing (in the March 1996 issue) whether or not premedical students know what they are facing.[1] The raw data presented in the article were not subjected to statistical quantitation, however, making them hard to interpret. For example, the statement that "far fewer than half" of the premedical students surveyed would be discouraged from pursuing a medical career because of the fear of being sued is misleading. Of the 84 premedical students surveyed, 32 indicated that they would be discouraged by the fear of being sued. When the z approximation and χ^2 tests are done, 32 of 84 is not significantly different from 42 of 84.[2] Alternatively, confidence limits can be calculated for the proportion 32 of 84. The 95% confidence interval for 32 of 84 (38%) ranges from 23 of 84 (27%) to 41 of 84 (49%) using the continuity correction.[3(p121)] Thus, by using statistics, it would be fair to say that "nearly half" of the premedical students would be discouraged from pursuing a medical career because of the fear of being sued. This is a much different conclusion than the one presented in the article. The area of Dr Chuck's research is highly intriguing, and thus it would be interesting to statistically quantitate the raw data before drawing any conclusions.

THOMAS F. HESTON, MD
Southwest Washington Medical Center
PO Box 1600
Vancouver, WA 98668

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Lessons From the Practice

Hypoglycemia in Bosnia

ROD HAMER, MD, *Santa Barbara, California*

During a recent overseas assignment, a general rule of medicine was reaffirmed for me: do not accept another physician's diagnosis at face value. As a volunteer to aid in the training of young physicians and nurses in an emergency department (ER) in central war-torn Bosnia, I had arrived just before 0800 for my first day. An interpreter introduced me to Dr Asim, a bright and "take-charge" resident. We toured the department, and I was pleased that he could communicate in halting English.

At the time, there was only one patient in the ER, an older man in his 60s. He lay passively on a gurney while an aged monitor's beep verified his being alive. "What is wrong with him?" I asked Dr Asim.

"Have 'strock,'" he replied.

"What will you do for his stroke?"

"Admit Neuropsychiatric Unit. He die," was the reply.

At the time, I was unaware that after a lengthy wait in the ER, the patient would be taken to the neuropsychiatric receiving room. There he would again wait for an admitting physician to do another assessment, delaying any treatment another four or more hours, if there were any treatment.

The ER tour finished, I had my first kava (coffee) break, which was a social event of high priority and frequency. A dozen or more physicians and nurses from several departments sat on beds and chairs, smoking, chatting, and sipping the silt-like Turkish coffee. The "strock" victim lay unattended in another room with no intravenous line, no oxygen, and no restraints to prevent his falling to the floor. As far as I could tell, they had "seen" him, made a disposition, and their attention to him had ended.

Driven off by secondhand smoke, I wandered back to the patient's bedside and, out of curiosity, examined him. There were some findings that seemed to negate Dr Asim's diagnosis. There was no facial droop, no limb weakness, and bilateral Babinski's were present. He was awake, and his eyes slowly followed me. I wondered about a more global neurologic problem such as a metabolic encephalopathy.

Dr Asim returned from the coffee festival and silently watched me. Was he upset about my snooping? Had I, having been there only half an hour, already offended him? I nonchalantly asked if a blood sugar determination was available. I was surprised when he said, "Sure," and then astonished when he said, "Take four hours."

I suggested we draw a blood specimen and send it off and then gambled with my chance of having my hunch validated. At my urging, a nurse administered 25 ml of a 50% dextrose solution. The response was dramatic. Like spinach to Popeye, the D50W bolus awakened the patient's hypoglycemic brain, and a few minutes later, he was asking for kava and a cigarette.

When the dramatic change in the patient occurred, the Bosnians gave me a round of applause and high-fives. Two younger men appeared at the bedside, amazed that their father was alive and greeting them. They had brought him to the ER, were told that he was dying, and they had gone to order a coffin, a commodity in great demand in Bosnia. The brothers confirmed the patient's previous diagnosis of diabetes and that the father self-injected a medicine each morning. Unaware of its relevance, they had not told the staff nor were they asked. Soon "Poppa" went home with them, his "strock" having resolved.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

(Hamer R: Hypoglycemia in Bosnia. West J Med 1996; 165:399)

From the Student Health Service, University of California, Santa Barbara.
Reprint requests to Robert Hamer, MD, 1114 Bel Air Dr, Santa Barbara, CA 93106.

AUTHOR INDEX

Abbey, David, Loma Linda, Calif (Sep) 140
Abbott, Sharon, Berkeley, Calif (Jul/Aug) 15
Agarwal, Sanjay K., Los Angeles, Calif (Dec) 392
Aminoff, Michael J., San Francisco,Calif (Oct) 248
Anderson, Arlyss L., San Francisco, Calif (Oct) 209
Anderson, Mark, Davis, Calif (Jul/Aug) 58
Andersson, Peter-Brian, San Francisco, Calif (Nov) 313
Auster, Simon, Bethesda, Md (Sep) 164

Baldeck, Mark, Albuquerque, NM (Jul/Aug) 57
Baron, Roy, Atlanta, Ga (Jul/Aug) 15
Barnett, Angela L., Albuquerque, NM (Sep) 144
Barrett, Mark F., Berkeley, Calif (Oct) 221
Barrett, Timothy J., Atlanta, Ga (Jul/Aug) 15
Beaudoin, Denise E., Salt Lake City, Utah (Oct) 192
Bennett, Charles L., Chicago, Ill (Jul/Aug) 37
Bennett, William M, Portland, Ore (Oct) 241
Berglund, David, Loma Linda, Calif (Sep) 140
Berriman, Diane, Loma Linda, Calif (Dec) 382
Birnbaum, Yochai, Los Angeles, Calif (Dec) 364
Bloom, Joseph D., Portland, Ore (Jul/Aug) 31
Bonow, Robert O., Chicago, Ill (Dec) 393
Bradley, Anne L., Nashville, Tenn (Nov) 318
Brant, William, Sacramento, Calif (Jul/Aug) 52
Brummel-Smith, Kenneth, Portland, Ore (Oct) 205
Bryant, Ray, Berkeley, Calif (Jul/Aug) 15
Buchwald, Dedra, Seattle, Wash (Nov) 289
Bull, David A., Salt Lake City, Utah (Dec) 379
Burnett, Cindy L., Salt Lake City, Utah (Oct) 192
Bushberg, Jerrold T, Sacramento, Calif (Nov) 301
Byrd, Gregory S., Aurora, Colo (Oct) 197

Cambron, Laurence D., Albuquerque, NM (Jul/Aug) 58
Cataldo, Renzo M., Salt Lake City, Utah (Dec) 379
Chaisson, Richard E., Baltimore, Md (Jul/Aug) 67
Chan, Stephanie Y., San Jose, Calif (Jul/Aug) 61
Chavez, Gilberto F., Sacramento, Calif (Jul/Aug) 20
Cheever, Laura W., Baltimore, Md (Jul/Aug) 67
Chen, Samuel M., Glendale, Calif (Oct) 254
Chin, Homer G., San Diego, Calif (Dec) 373
Chong, Brian W., Sacramento, Calif (Jul/Aug) 53
Chu, Lawrence D., Los Angeles, Calif (Sep) 119
(Dec) 398

Clark, Orlo H., San Francisco, Calif (Sep) 131
Clark-Sayles, Catherine , Mill Valley, Calif (Sep) 204
Clever, Linda Hawes, San Francisco, Calif (Sep) 159
Coffman, Janet M., San Francisco, Calif (Oct) 246
Collier, Ann C., Seattle, Wash (Nov) 289
Cone, Lawrence A., Rancho Mirage, Calif (Nov) 322
Conley, Christopher D., Ann Arbor, Mich (Nov) 311

Dales, Loring G., Berkeley, Calif (Jul/Aug) 80
Dales, Robert E., Ottawa, Ont (Sep) 157
Dansky, Laura, San Francisco, Calif (Sep) 112
Davidson, Terence M., San Diego, Calif (Oct) 252
Day, John D., Stanford, Calif (Jul/Aug) 64
Diggles, Linda, Torrance, Calif (Nov) 302
De Doncker, Piet, Beerse, Belgium (Dec) 349
Del Gianni, Teresa, Seattle, Wash (Dec) 352
Dower, Catherine M., San Francisco, Calif (Oct) 246

Eghtesad, Bijan, Albuquerque, NM (Sep) 144
Ellis, Arthur A., Sacramento, Calif (Jul/Aug) 20
Ellison, Kristin E., Stanford, Calif (Jul/Aug) 64
Ey, Stephen R., Corona Del Mar, Calif (Oct) 227

Feldstein, Vickie A., San Francisco, Calif (Jul/Aug) 56
Finocchio, Leonard J., San Francisco, Calif (Oct) 246
Firek, Anthony F., Loma Linda, Calif, (Dec) 382

Gallant, Joel E., Baltimore, Md (Jul/Aug) 67
Ganzini, Linda, Portland, Ore (Oct) 205
Gare, Meir, Chicago, Ill (Oct) 231
Gates, Robert H. Jr., Aurora, Colo (Oct) 197
Gilliss, Catherine L., San Francisco, Calif (Oct) 209
Ginsberg, Michele, San Diego, Calif (Jul/Aug) 15
Girard, Donald E., Portland, Ore (Jul/Aug) 31
Glasgow, Robert E., San Francisco, Calif (Nov) 294
Godil, Aslam, Loma Linda, Calif (Dec) 382
Godil, Fouzia, Victorville, Calif (Dec) 382
Goldberg, James D., San Francisco, Calif (Dec) 376
Goldstein, Erika, Seattle, Wash (Nov) 289,324
Goodkin, Donald E., San Francisco, Calif (Nov) 313
Grebe, Stefan K.G., Rochester, Minn (Sep) 156
Gregory, Martin C., Salt Lake City, Utah (Dec) 379
Griffin, Patricia M., Atlanta, Ga (Jul/Aug) 15
Gupta, Aditya K., Toronto, Ont (Dec) 349
Gutman, Alisa, Jerusalem, Israel (Oct) 231
Gyetvai, Erno J., Sacramento, Calif (Nov) 301

Hamer, Rod, Santa Barbara, Calif (Dec) 399
Harber, Philip, Los Angeles, Calif (Sep) 142
Hardee, James T., Albuquerque, NM (Sep) 144
Hay, Ian D., Rochester, Minn (Sep) 156
Heimbach, David, Seattle, Wash (Oct) 215
Heston, Thomas F., Vancouver, Wash (Dec) 398
Hickam, David H., Portland, Ore (Jul/Aug) 26
Hill, Linda, San Diego, Calif (Oct) 224
Himelman, Ronald B., Rancho Mirage, Calif (Nov) 322
Hirschberg, Joel N., Rancho Mirage, Calif (Nov) 322
Hooton, Thomas M., Seattle, Wash (Nov) 289
Howard, Robin S., Washington, DC (Oct) 197
Hulett, Rebecca, Tucson, Ariz (Jul/Aug) 54
Hutcheson, Joseph W., Rancho Mirage, Calif (Nov) 322

Iacopino, Vincent, San Francisco, Calif (Sep) 112

Jacobs, Jeffrey, Emeryville, Calif (Nov) 283
Jamal, M. Mazen, Albuquerque, NM (Sep) 144
Janson, Susan, San Francisco, Calif (Sep) 149
Jensen, William A., San Jose, Calif (Jul/Aug) 61
Jeppson, Lew, Salt Lake City, Utah (Oct) 192
Jonsen, Albert R., Seattle, Wash (Oct) 250
Judd, Howard L., Los Angeles, Calif (Dec) 392

Keller, Thomas M., Oakland, Calif (Nov) 279
Ketai, Loren, Albuquerque, NM (Jul/Aug) 57
Khalkhali, Ira J., Torrance, Calif (Nov) 302
Kilman, Liga, Los Angeles, Calif (Sep) 126
Kirsch, Carl M., San Jose, Calif (Jul/Aug) 61
Kith, Phalla, Seattle, Wash (Nov) 289
Kloner, Robert A., Los Angeles, Calif (Dec) 364
Knapik, Steve, Victorville, Calif (Dec) 382
Koo, Denise, Atlanta, Ga (Jul/Aug) 15
Kowdley, Kris V., Seattle, Wash (Oct) 229
Kramer, Vicki L., Berkeley, Calif (Oct) 224
Kreutzer, Richard, Emeryville, Calif (Nov) 283
Krupp, Lauren B., Stony Brook, NY (Nov) 320

Larson, David A., San Francisco, Calif (Jul/Aug) 59
Lee, Makau, San Antonio, Texas (Nov) 308
Lee, Melinda A., Portland, Ore (Oct) 205
Leistikow, Bruce N., Davis, Calif (Sep) 139
(Oct) 226

Litwin, Sheldon E., Salt Lake City, Utah (Dec) 379
Lukehart, Sheila A., Seattle, Wash (Nov) 289

McCann, Ulysse G. II, San Antonio, Texas (Nov) 308
McCormack, Bruce M., San Francisco, Calif (Jul/Aug) 43
McDermott, Michael W., San Francisco, Calif (Jul/Aug) 59
Main, Elliot K., San Francisco, Calif (Dec) 372
Malcolm, George B., Atlanta, Ga (Sep) 126

Mann, Roberta, Seattle, Wash . . . (Oct) 215
Mannino, Elizabeth, San Diego, Calif . . . (Oct) 224
Marinella, Mark A., Dayton, Ohio . . . (Sep) 161
(Nov) 311
Marks, Melinda L., Salt Lake City, Utah . . . (Dec) 379
Mascola, Laurene, Los Angeles, Calif . . . (Sep) 126
Matthews, Annette M., Portland, Ore . . . (Jul/Aug) 31
Matthews, Elizabeth T., Albuquerque, NM . . . (Oct) 253
Mazur, Dennis J., Portland, Ore . . . (Jul/Aug) 26
Meador, Jody, Santa Ana, Calif . . . (Sep) 140
Millard, Peter S., Bangor, Maine . . . (Nov) 323
Mintz, Eric D., Atlanta, Ga . . . (Jul/Aug) 15
Mishkin, Fred, Torrance, Calif . . . (Nov) 303
Montauk, Lance, Berkeley, Calif . . . (Sep) 163
Moore, Douglas, Santa Ana, Calif . . . (Sep) 140
Morse, Linda H., San Francisco, Calif . . . (Jul/Aug) 83
Mulvihill, Sean J., San Francisco, Calif . . . (Nov) 294

Nachtigall, Robert D., San Francisco, Calif . . . (Dec) 373
Nelson, Anita L., Manhattan Beach, Calif . . . (Dec) 374
Nelson, Heidi D., Portland, Ore . . . (Jul/Aug) 31
Ng, Don C., San Francisco, Calif . . . (Oct) 234
Nitta, Annette, Los Angeles, Calif . . . (Oct) 225
Nolan, Charles R. III, San Antonio, Texas . . . (Nov) 308
Norman, Michael, Victorville, Calif . . . (Dec) 382

O'Neil, Edward H., San Francisco, Calif . . . (Oct) 246
Oppenheim, Elliott B., Grosse Point, Mich . . . (Jul/Aug) 85

Passaro, Douglas J., Berkeley, Calif . . . (Sep) 126
Patchin, Rebecca J., Loma Linda, Calif . . . (Oct) 245
Patel, Maitray D., San Francisco, Calif . . . (Jul/Aug) 56
Paulson, Richard J., Los Angeles, Calif . . . (Dec) 377
Pei, Gloria K., Hong Kong . . . (Jul/Aug) 37
Perlroth, Mark G., Stanford, Calif . . . (Jul/Aug) 64
Peterson, Norman E., Denver, Colo . . . (Sep) 161
Pinson, C. Wright, Nashville, Tenn . . . (Nov) 318
Purdy, Laurence J., Pomona, Calif . . . (Sep) 154

Rabito, Felix, San Antonio, Texas . . . (Nov) 308
Raghu, Ganesh, Seattle, Wash . . . (Dec) 355
Reed, William W., Honolulu, Hawaii . . . (Oct) 197
Reiter, Gary S., Holyoke, Mass . . . (Jul/Aug) 84
Reporter, Roshan, Los Angeles, Calif . . . (Sep) 126
Reus, Victor I., San Francisco, Calif . . . (Jul/Aug) 83
Rheinberger, Marguerite M., Atlanta, Ga . . . (Oct) 192
Robin, Nathaniel H., Cleveland, Ohio . . . (Nov) 326
Rolka, Henry, Atlanta, Ga . . . (Sep) 126
Robertson, William O., Seattle, Wash . . . (Dec) 352
Rosenberg, Robert, Albuquerque, NM . . . (Jul/Aug) 58
Rowbotham, Michael C., San Francisco, Calif . . . (Sep) 147
Rupp, Frederick W., Albuquerque, NM . . . (Jul/Aug) 53
Russi, M. Francis, San Jose, Calif . . . (Sep) 161
Rutherford, George W., Berkeley, Calif . . . (Oct) 221

Sakiyama, Roland, Los Angeles, Calif . . . (Dec) 386
Salpeter, Shelley R., San Jose, Calif . . . (Nov) 323
Sauder, Daniel N., Toronto, Ont . . . (Dec) 349
Scher, Richard K., New York, NY . . . (Dec) 349
Schnittger, Ingela, Stanford, Calif . . . (Jul/Aug) 64
Schriger, David L., Los Angeles, Calif . . . (Jul/Aug) 74
Sell, James J., Albuquerque, NM . . . (Jul/Aug) 53
Seward, James P., Berkeley, Calif . . . (Oct) 222
Shah, Misha, San Antonio, Texas . . . (Nov) 308
Shalit, Meir, Jerusalem, Israel . . . (Oct) 231
Shear, Neil H., Toronto, Ont . . . (Dec) 349
Shefer, Abigail, Atlanta, Ga . . . (Jul/Aug) 15
Shelton, David K., Sacramento, Calif . . . (Jul/Aug) 53
(Nov) 303
Sherck, John, San Jose, Calif . . . (Jul/Aug) 61
Shore, James H., Denver, Colo . . . (Jul/Aug) 81
Shusterman, Dennis, San Francisco, Calif . . . (Sep) 141
Smith, Natalie J., Berkeley, Calif . . . (Jul/Aug) 80
Sniezek, Joseph E., Atlanta, Ga . . . (Oct) 192
Sorenson, Susan B., Los Angeles, Calif . . . (Sep) 119
(Dec) 398
Sprung, Robert F., Salt Lake City, Utah . . . (Dec) 379
Stadalnik, Robert C., Sacramento, Calif . . . (Nov) 303
Stolinsky, David C., Los Angeles, Calif . . . (Dec) 397
Sutter, Charles W., Sacramento, Calif . . . (Nov) 301

Tait, Karen M., Colusa, Calif . . . (Oct) 245
Taylor, Kirk, San Francisco, Calif . . . (Sep) 147
Telepak, Robert J., Albuquerque, NM . . . (Jul/Aug 53
Thannoun, Abdul, Albuquerque, NM . . . (Sep) 144
Thurman, David J., Atlanta, Ga . . . (Oct) 192
Tung, Bruce Y., Seattle, Wash . . . (Oct) 229

Ultmann, John E., Chicago, Ill . . . (Jul/Aug) 37

Vasudevan, Priya, Seattle, Wash . . . (Dec) 352
Vogel, John M., Sacramento, Calif . . . (Nov) 304
Von Behren, Julie, Emeryville, Calif . . . (Nov) 283
Vugia, Duc J., Berkeley, Calif . . . (Sep) 126
(Oct) 224

Waterman, Stephen H., Berkeley, Calif . . . (Jul/Aug) 80
Waxman, Alan D., Los Angeles, Calif . . . (Nov) 305
Weaver, Michael J., Aurora, Colo . . . (Oct) 197
Weinstein, Harvey M., San Francisco, Calif . . . (Sep) 112
Weinstein, Phillip R., San Francisco, Calif . . . (Jul/Aug) 43
Weismuller, Penny, Santa Ana, Calif . . . (Sep) 140
Wells, Joy G., Atlanta, Ga . . . (Jul/Aug) 15
Werner, S. Benson, Berkeley, Calif . . . (Jul/Aug 15
(Sep) 126
Westra, Sjirk J., Los Angeles, Calif . . . (Jul/Aug) 55
Wheeler, Donald, Albuquerque, NM . . . (Sep) 144
Wilcosky, Timothy C., Research Triangle Park, NC . . (Nov) 323
Wilkes, Michael S., Los Angeles, Calif . . . (Jul/Aug) 74
Williamson, Michael R., Albuquerque, NM . . . (Jul/Aug) 58
Wise, Samuel A., Las Vegas, Nev . . . (Oct) 252
Wood, Douglas E., Seattle, Wash . . . (Dec) 355
Wyatt, Rhonda A., Fairfield, Calif . . . (Nov) 306

Yoder, Laurie, San Francisco, Calif . . . (Oct) 209

IN MEMORIAM

California Medical Association

Acton, William E., May 7, 1996 . . . (Jul/Aug) 14
Andrews, Alan V., Oct 6, 1996 . . . (Dec) 407
Ascher, David S., May 17, 1996 . . . (Jul/Aug) 14
Bailey, Douglas A., Jan 22, 1996 . . . (Dec) 407
Birch, Ronald Stuart, May 24, 1996 . . . (Sep) 165
Bronson, Jeffrey Lawrence, Jun 14, 1996 . . . (Jul/Aug) 14
Busby, Dennis R., Jun 22, 1996 . . . (Jul/Aug) 14
Chapman, Ethel A., Aug 21, 1996 . . . (Sep) 165
Coger, Charles W., Aug 29, 1996 . . . (Dec) 407
Conforth, Elizabeth L., Jul 26, 1996 . . . (Sep) 165
Crown, Ronald F., Oct 10, 1996 . . . (Dec) 407
Curry, Francis, Aug 3, 1996 . . . (Sep) 165
Derey, Kevin, Aug 21, 1996 . . . (Dec) 407
Dunford, Ruth, Aug 23, 1996 . . . (Sep) 165
Fish, Victor J., Jan 1, 1996 . . . (Dec) 407
George, Ralph P., Jun 2, 1996 . . . (Sep) 165
Goetsch, Carl, Jul 3, 1996 . . . (Jul/Aug) 14
Green, Robert S., Feb 14, 1996 . . . (Jul/Aug) 14
Green, Walter, Aug 7, 1996 . . . (Sep) 165
Hamilton, George R., Jul 10, 1995 . . . (Dec) 407
Hanshaw, Truman R., Jan 3, 1995 . . . (Dec) 407
Hodge, James J., Jun 24, 1996 . . . (Jul/Aug) 14
Jamison, Ellis T., Jun 1, 1994 . . . (Dec) 407
Johnson, Francis T., Mar 5, 1996 . . . (Jul/Aug) 14
Johnson, Kenneth M., Jun 26, 1996 . . . (Jul/Aug) 14
Kaufman, Paul, Jun 15, 1996 . . . (Sep) 165
Kelenscher, Alan J., Jul 29, 1996 . . . (Sep) 165
Kelly, William L., Jan 21, 1996 . . . (Jul/Aug) 14
Kinsman, Robert G., Jun 4, 1996 . . . (Jul/Aug) 14
Kirklin, Ashley R., Jul 21, 1996 . . . (Sep) 165
Kleinhenz, Robert Joseph, Aug 4, 1996 . . . (Sep) 165

Ledwich, Thomas W., Jun 2, 1996 . . . . . (Jul/Aug) 14
Lizardi, Hector, Nov 2, 1996 . . . . . (Jul/Aug) 14
Mari, Phadej, Jul 1996 . . . . . (Dec) 407
Millar, Glenn C., Jul 15, 1996 . . . . . (Jul/Aug) 14
Milligan, Joseph R., Sep 27, 1996 . . . . . (Dec) 407
Morel, J. Felix, Jun 8, 1996 . . . . . (Sep) 165
Paulson, Frank, Jun 15, 1996 . . . . . (Dec) 407
Rajala, A. I., Jun 24, 1996 . . . . . (Jul/Aug) 14
Rath, Richard A., Jun 16, 1996 . . . . . (Dec) 407
Roach, Robert W., Jun 1996 . . . . . (Jul/Aug) 14
Rothenberg, Sam, Dec 20, 1994 . . . . . (Dec) 407
Rubenstein, Martin, Nov 11, 1996 . . . . . (Dec) 407
Seibert, Warren, Nov 8, 1996 . . . . . (Dec) 407
Seleski, George A., May 24, 1996 . . . . . (Jul/Aug) 14
Stafford, Richard L., May 13, 1996 . . . . . (Jul/Aug) 14
Sterling, Allen F., Oct 6, 1996 . . . . . (Dec) 407
Vigo, Anthony, Jun 14, 1996 . . . . . (Jul/Aug) 14
Ward, Walter, Mar 26, 1996 . . . . . (Jul/Aug) 14
Williams, S. Randall, Jul 22, 1996 . . . . . (Jul/Aug) 14
Winchester, William W., Jul 20, 1996 . . . . . (Dec) 407
Wong, Louise May, Oct 22, 1996 . . . . . (Dec) 407
Young, John E., Sep 9, 1996 . . . . . (Dec) 407
Zetterlund, Russell P., May 31, 1996 . . . . . (Jul/Aug) 14

New Mexico Medical Society
Baker, Maria L., Jul 9, 1996 . . . . . (Jul/Aug) 14
Miller, Eric R., May 15, 1996 . . . . . (Jul/Aug) 14
Spitz, Theodore, Jul 3, 1996 . . . . . (Jul/Aug) 14

SUBJECT INDEX

A

Academic Physicians, Clinical Investigators, and Managed Care—Whither Hippocrates? William M. Bennett . . . . . (Oct) 241
Action Plans in Asthma Management—Why, When, and How? (Topics in Primary Care Medicine), Susan Janson. . (Sep) 149
Editorial, Robert E. Dales . . . . . (Sep) 157
Acute Renal Failure Complicating Nonfulminant Hepatitis A (Alerts, Notices, and Case Reports), Ulysse G. McCann II, Felix Rabito, Misha Shah, Charles R. Nolan III, Makau Lee. . . . . (Nov) 308
Adolescent Contraception, Anita L. Nelson . . . . . (Dec) 374
Advances in the Treatment of Multiple Sclerosis (Editorial), Lauren B. Krupp. . . . . (Nov) 320
Androgen Replacement in Postmenopausal Women, Homer G. Chin . . . . . (Dec) 373
Asthma Management—A Call for Action (Editorial), Robert E. Dales . . . . . (Sep) 157
Assisted Reproductive Technologies, Richard J. Paulson . . . . . (Dec) 377

Alerts, Notices, and Case Reports

Acute Renal Failure Complicating Nonfulminant Hepatitis A, Ulysse G. McCann II, Felix Rabito, Misha Shah, Charles R. Nolan III, Makau Lee. . . . . (Nov) 308
Diabetic Neuropathic Cachexia, Aslam Godil, Diane Berriman, Steve Knapik, Michael Norman, Fouzia Godil, Anthony F. Firek. . . . . (Dec) 382
Intussusception in an Adult, Mark A. Marinella, Christopher D. Conley . . . . . (Nov) 311
Lysinuric Protein Intolerance Presenting as Coma in a Middle-Aged Man, Meir Gare, Meir Shalit, Alisa Gutman. . . . . (Oct) 231
Propylthiouracil-Induced Hepatotoxicity, James T. Hardee, Angela L. Barnett, Abdul Thannoun, Bijan Eghtesad, Donald Wheeler, M. Mazen Jamal. . . . . (Sep) 144
Ruptured Sinus of Valsalva Aneurysm in a Patient With Autosomal Dominant Polycystic Kidney Disease, Robert F. Sprung, Renzo M. Cataldo, Martin C. Gregory, Melinda L. Marks, David A. Bull., Sheldon E. Litwin, ... (Dec) 379
Spontaneous Group B Streptococcal Meningitis in a Patient With Cirrhosis, Bruce Y. Tung, Kris V. Kowdley. . . (Oct) 229
Tension Pneumoperitoneum, Stephanie Y. Chan, Carl M. Kirsch, William A. Jensen, John Sherck . . . . . (Jul/Aug) 61
Venlafaxine Hydrochloride and Chronic Pain, Kirk Taylor, Michael C. Rowbotham. . . . . (Sep) 147
Wegener's Granulomatosis Presenting as Dilated Cardiomyopathy John D. Day, Kristin E. Ellison, Ingela Schnittger, Mark G. Perlroth . . . . . (Jul/Aug) 64

Approach to Patients With Hirsutism (Topics in Primary Care Medicine), Roland Sakiyama . . . . . (Dec) 386
Editorial, Sanjay K. Agarwal, Howard L. Judd . . . . (Dec) 392
Assisted Suicide, see *When Patients Ask About*
Asthma Management—A Call for Action (Editorial), Robert E. Dales . . . . . (Sep) 157
Avoiding Medication Mixups—Identifiable Imprint Codes, Priya Vasudevan, Teresa Del Gianni, William O. Robertson, ... (Dec) 352

B

Barriers to Practice: Reality or Perception? (Editorial) Karen M. Tait, Rebecca J.Patchin . . . . . (Oct) 245
Broken Promise (Commentary), Laurence J. Purdy . . . . (Sep) 154

C

California's 1988–1991 Measles Epidemic—The Last One? (Editorial), Natalie J. Smith, Loring G. Dales, Stephen H. Waterman . . . . . (Jul/Aug) 80
Cardiomyopathy, see *Wegener's Granulomatosis Presenting as Dilated*
Caution: The Meter Is Running—Informing Patients About Health Care Costs (Commentary), Michael S. Wilkes, David L. Schriger . . . . . (Jul/Aug) 74
A Cluster of *Escherichia coli* O157:H7 Infections With the Hemolytic-Uremic Syndrome and Death in California—A Mandate for Improved Surveillance, Abigail M. Shefer, Denise Koo, S. Benson Werner, Eric D. Mintz, Roy Baron, Joy G. Wells, Timothy J. Barrett, Michele Ginsberg, Ray Bryant, Sharon Abbott, Patricia M. Griffin. . . . (Jul/Aug) 15
Cervical Spondylosis—An Update (Conferences and Reviews), Bruce M. McCormack, Phillip R. Weinstein . . . . . (Jul/Aug) 43
Cholescintigraphy in Acute and Chronic Gallblader Dysfunction, David K. Shelton, Robert C. Stadalnik . . . . . (Nov) 303
Collimation Approaches to 511-keV Imaging, Alan D. Waxman . . . . . (Nov) 305

Commentary

Academic Physicians, Clinical Investigators, and Managed Care—Whither Hippocrates? William M. Bennett . . . . . (Oct) 241
Broken Promise, Laurence J. Purdy. . . . . (Sep) 154
Caution: The Meter Is Running—Informing Patients About Health Care Costs, Michael S. Wilkes, David L. Schriger . . . . . (Jul/Aug) 74

Conferences and Reviews

Cervical Spondylosis—An Update Bruce M. McCormack, Phillip R. Weinstein . . . . . (Jul/Aug) 43
Hospital Volume Influences Outcome in Patients Undergoing Pancreatic Resection for Cancer, Robert E. Glasgow, Sean J. Mulvihill . . . . . (Nov) 294
Lung Transplantation—Part I. Indications and Operative Management, Douglas E. Wood, Ganesh Raghu . . . (Dec) 355
Myocardial Viability, Yochai Birnbaum, Robert A. Kloner . . . . . (Dec) 364
Editorial, Robert O. Bonow . . . . . (Dec) 393
Predictors of Thyroid Tumor Aggressiveness, ... Orlo H. Clark . . . . . (Sep) 131
Editorial, Stefan K.G. Grebe, Ian D. Hay . . . . . (Sep) 156
Prognosis and Treatment of Burns, Roberta Mann, David Heimbach. . . . . (Oct) 215

Correspondence

Do Premedical Students Fear Being Sued?, Thomas F. Heston . . . (Dec) 398
Female Prostatitis? Norman E. Peterson . . . (Sep) 161
M. Francis Russi . . . (Sep) 161
Genetics and Homosexuality, Linda H. Morse . . . (Jul/Aug) 83
Response, Victor I. Reus . . . (Jul/Aug) 83
Isoniazid-Related Fatal Hepatitis, Shelley R. Salpeter . . (Nov) 323
Response, Peter S. Millard, Timothy C. Wilcosky . . (Nov) 323
Itraconazole-Related Amaurosis and Vomiting Due to Digoxin Toxicity, Lawrence A. Cone, Ronald B. Himelman, Joel N. Hirschberg, Joseph W. Hutcheson . . . (Nov) 322
Jarisch-Herxheimer Reaction, Mark A. Marinella . . . (Sep) 161
Out-of-Control Snowboarders, Samuel A. Wise . . . (Oct) 252
Response, Terence M. Davidson . . . (Oct) 252
Violence in America, David C. Stolinsky . . . (Dec) 397
Response, Susan B. Sorenson, Lawrence D. Chu . . (Dec) 398

Courage (Lessons From the Practice), Anonymous . . . . (Jul/Aug) 86
Current Pharmacologic Treatment of Multiple Sclerosis Symptoms (Topics in Primary Care Medicine), Peter-Brian Andersson, Donald E. Goodkin . . . (Nov) 313
Editorial, Lauren B. Krupp . . . (Nov) 320
Current Status of Thrombolysis, James J. Sell, Frederick W. Rupp, Robert J. Telepak . . . (Jul/Aug) 53

D

Decreasing Work Ability From Asthma, Philip Harber . . (Sep) 142
Detection and Localization of Gastrointestinal Bleeding, Rhonda A. Wyatt . . . (Nov) 306
Diabetic Neuropathic Cachexia (Alerts, Notices, and Case Reports), Aslam Godil, Diane Berriman, Steve Knapik, Michael Norman, Fouzia Godil, Anthony F. Firek . . (Dec) 382
Directly Observed Therapy for Tuberculosis, Elizabeth Mannino, Linda Hill . . . (Oct) 224
Do Premedical Students Fear Being Sued?, Thomas F. Heston . . . (Dec) 398
Doppler Ultrasonography of Transjugular Intrahepatic Portosystemic Shunts, Vickie A. Feldstein, Maitray D. Patel . . . (Jul/Aug) 56

E

Editorials

Advances in the Treatment of Multiple Sclerosis, Lauren B. Krupp . . . (Nov) 320
Asthma Management—A Call for Action, Robert E. Dales . . . (Sep) 157
Barriers to Practice—Reality or Perception? Karen M. Tait, Rebecca J. Patchin . . . (Oct) 245
California's 1988–1991 Measles Epidemic—The Last One? Natalie J. Smith, Loring G. Dales, Stephen H. Waterman . . . (Jul/Aug) 80
A Guide of the Perplexed—Assisted Suicide, Albert R. Jonsen . . . (Oct) 250
The Order of the Day? Cheers, Thanks, and Introductions, Linda H. Clever . . . (Sep) 159
Parkinson's Disease—A Progress Report, Michael J. Aminoff . . . (Oct) 248
Physicians and Nurse Practitioners—Old Conflicts and New Opportunities, Leonard J. Finocchio, Janet M. Coffman, Catherine M. Dower, Edward H. O'Neil . . . (Oct) 246
A Primer for Clinicians on Mushroom Poisoning in the West, C. Wright Pinson, Anne L. Bradley . . . (Nov) 318
Prognostic Factors and Management in Thyroid Cancer—Consensus or Controversy? Stefan K.G. Grebe, Ian D. Hay . . . (Sep) 156
Progress in Treatments for Substance-Impaired Physicians James H. Shore . . . (Jul/Aug) 81
The Search for Viable Myocardium, Robert O. Bonow . (Dec) 393
What We See Most, We Understand Least, Sanjay K. Agarwal, Howard L. Judd . . . (Dec) 392

Epidemic *Salmonella enteritidis* Infection in Los Angeles County, California—The Predominance of Phage Type 4, Douglas J Passaro, Roshan Reporter, Laurene Mascola, Liga Kilman, George B. Malcolm, Henry Rolka, S. Benson Werner, Duc J. Vugia . . . (Sep) 126
Epidemiology and Control of Coccidioidomycosis in California, George W. Rutherford, Mark F. Barrett . . . (Oct) 221

Epitomes

Nuclear Medicine
Cholescintigraphy in Acute and Chronic Gallbladder Dysfunction, David K. Shelton, Robert C. Stadalnik . . . (Nov) 303
Collimation Approaches to 511-keV Imaging, Alan D. Waxman . . . (Nov) 305
Detection and Localization of Gastrointestinal Bleeding, Rhonda A. Wyatt . . . (Nov) 306
Radiation Synovectomy, Erno J. Gyetvai, Charles W. Sutter . . . (Nov) 301
Radiodosimetry in Nuclear Medicine, Jerrold T. Bushberg . . . (Nov) 301
Role of Lung Scanning in Patients With Pulmonary Embolism, Fred Mishkin . . . (Nov) 303
Scintimammography—A New Tool for Breast Cancer Diagnosis, Ira J. Khalkhali, Linda Diggles . . . (Nov) 302
Use of Bone Mineral Measurements in the Management of Osteoporosis, John M. Vogel . . . (Nov) 304

Obstetrics and Gynecology
Adolescent Contraception, Anita L. Nelson . . . (Dec) 374
Androgen Replacement in Postmenopausal Women, Homer G. Chin . . . (Dec) 373
Assisted Reproductive Technologies, Richard J. Paulson . . . (Dec) 377
Intracytoplasmic Sperm Injection, Robert D. Nachtigall . . . (Dec) 373
Managing Viral Exposure During Pregnancy, James. D. Goldberg . . . (Dec) 376
Prematurity—Steroids for All, Elliott K. Main . . . (Dec) 372

Occupational Medicine
Decreasing Work Ability From Asthma, Philip Harber . . (Sep) 142
Latex Allergy, Dennis Shusterman . . . (Sep) 141
Long-term Effects of Air Pollution, David Berglund, David Abbey . . . (Sep) 140
Preventing Workers' Hepatitis A, B, C, D, E, and G, Bruce N. Leistikow . . . (Sep) 139
Use of Nucleic Acid in the Diagnosis and Management of Tuberculosis Amplification Tests, Jody Meador, Douglas Moore, Penny Weismuller . . . (Sep) 140

Preventive Medicine and Public Health
Directly Observed Therapy for Tuberculosis, Elizabeth Mannino, Linda Hill . . . (Oct) 224
Epidemiology and Control of Coccidioidomycosis in California, George W. Rutherford, Mark F. Barrett . . . (Oct) 221
Human Babesiosis and Ehrlichioses—Emerging Tick-Borne Diseases, Duc J. Vugia, Vicki L. Kramer . . . (Oct) 224
Multidrug-Resistant Tuberculosis—How Far Are We From New York City? Annette T. Nitta . . . (Oct) 225
Naltrexone Hydrochloride Use in the Treatment of Alcoholism, Stephen R. Ey . . . (Oct) 227
Occupational Lead Exposure and Management, James P. Seward . . . (Oct) 222
Smoking Cessation—New Challenges and Opportunities, Bruce N. Leistikow . . . (Oct) 226

Radiology
Current Status of Thrombolysis, James J. Sell, Frederick W. Rupp, Robert J. Telepak . . . (Jul/Aug) 53
Doppler Ultrasonography of Transjugular Intrahepatic Portosystemic Shunts, Vickie A. Feldstein,

Maitray D. Patel . . . . . (Jul/Aug) 56
Imaging of Appendicitis, Rebecca Hulett. . . . . (Jul/Aug) 54
Magnetic Resonance Imaging, Positron Emission Tomography, and Single-Proton-Emission Computed Tomography in Epilepsy, Brian W. Chong, David K. Shelton . . . (Jul/Aug) 53
Magnetic Resonance Imaging of Radiographically Occult Bony Trauma, Mark Anderson . . . . . (Jul/Aug) 58
Magnetic Resonance Imaging of the Breast, Robert Rosenberg, Laurence D. Cambron, Michael R. Williamson. . . . (Jul/Aug) 58
Percutaneous Core Biopsy of the Breast, William Brant. . . . . (Jul/Aug) 52
Radiosurgery, David A. Larson, Michael W. McDermott. . . . . (Jul/Aug) 59
Spiral and Ultrafast Computed Tomography for Noninvasive Cardiac Imaging in Children, Sjirk J. Westra . . . . . (Jul/Aug) 55
Spiral Computed Tomography and Magnetic Resonance Imaging in the Detection of Pulmonary Emboli, Mark Baldeck, Loren Ketai . . . . . (Jul/Aug) 57

Escherichia coli O157:H7 Infections With the Hemolytic-Uremic Syndrome and Death in California, see *Cluster of*
Evaluation of Cerebrospinal Fluid in Southeast Asian Refugees With Reactive Serologic Tests for Syphilis, Dedra Buchwald, Ann C. Collier, Sheila A. Lukehart, Phalla Kith, Erika Goldstein, Thomas M. Hooton. . . . . (Nov) 289
The Extra Window (Lessons from the Practice), Lance Montauk. . . . . (Sep) 163

F

Female Prostatitis? (Correspondence)
Norman E. Peterson . . . . . (Sep) 161
M. Francis Russi. . . . . (Sep) 161

G

Genetics and Homosexuality (Correspondence), Linda H. Morse . . . . . (Jul/Aug) 83
Response, Victor I. Reus. . . . . (Jul/Aug) 83
Gloria! . . .Glooooria! (Lessons From the Practice), Elliott B. Oppenheim . . . . . (Jul/Aug) 85
A Guide of the Perplexed—Assisted Suicide (Editorial), Albert R. Jonsen. . . . . (Oct) 250

H

Health Care Costs, see *Caution, the Meter Is Running—Informing Patients About*
Hemolytic-Uremic Syndrome and Death in California, see *Cluster of* Escherichia coli *O157:H7 Infections With the*
Homosexuality, see *Genetics and*
Hong Kong Health Care System, see *Western Impressions of*
Hospital Volume Influences Outcome in Patients Undergoing Pancreatic Resection for Cancer (Conferences and Reviews), Robert E. Glasgow, Sean J. Mulvihill . . . . . (Nov) 294
Human Babesiosis and Ehrlichioses—Emerging Tick-Borne Diseases, Duc J. Vugia, Vicki L. Kramer. . . . . (Oct) 224
Human Immunodeficiency Virus, see *Prophylaxis Against Opportunistic Infections in Patients Infected With the*
Hypoglycemia in Bosnia (Lessons From the Practice), Rod Hamer. . . . . (Dec) 399

I

I Owe It All to Jose and His Mother (Lessons From the Practice), Elizabeth T. Matthews . . . . . (Oct) 253
Imaging of Appendicitis, Rebecca Hulett. . . . . (Jul/Aug) 54
Informing Patients About Health Care Costs, see *Caution, the Meter Is Running*
Intracytoplasmic Sperm Injection, Robert D. Nachtigall. . . . . (Dec) 373
Intussusception in an Adult (Alerts, Notices, and Case Reports), Mark A. Marinella, Christopher D. Conley . . . . . (Nov) 311
Isoniazid-Related Fatal Hepatitis (Correspondence), Shelley R. Salpeter . . . . . (Nov) 323
Response, Peter S. Millard, Timothy C. Wilcosky . . (Nov) 323
Itraconazole-Related Amaurosis and Vomiting Due to Digoxin Toxicity (Correspondence), Lawrence A. Cone, Ronald B. Himelman, Joel N. Hirschberg, Joseph W. Hutcheson . . . . . (Nov) 322

J

Jarisch-Herxheimer Reaction (Correspondence), Mark A. Marinella . . . . . (Sep) 161

L

Latex Allergy, Dennis Shusterman. . . . . (Sep) 141

Lessons From the Practice

Courage, Anonymous . . . . . (Jul/Aug) 86
The Extra Window, Lance Montauk . . . . . (Sep) 163
Gloria! . . . Glooooria!, Elliott B. Oppenheim . . . . . (Jul/Aug) 85
Hypoglycemia in Bosnia, Rod Hamer . . . . . (Dec) 399
I Owe It All to Jose and His Mother, Elizabeth T. Matthews . . . . . (Oct) 253
Mrs O'Brien's Story, Gary S. Reiter . . . . . (Jul/Aug) 84
Myopia Revisited, Samuel M. Chen . . . . . (Oct) 254
Nursing and Doctoring, Erika Goldstein . . . . . (Nov) 324
Relations, Nathaniel H. Robin. . . . . (Nov) 326
Selective Deafness, Simon Auster . . . . . (Sep) 164

Long-term Effects of Air Pollution, David Berglund, David Abbey. . . . . (Sep) 140
Lung Transplantation—Part I. Indications and Operative Management (Conferences and Reviews), Douglas E. Wood, Ganesh Raghu . . . . . (Dec) 355
Lysinuric Protein Intolerance Presenting as Coma in a Middle-Aged Man (Alerts, Notices, and Case Reports), Meir Gare, Meir Shalit, Alisa Gutman . . . . . (Oct) 231

M

Magnetic Resonance Imaging of the Breast, Robert Rosenberg, Laurence D. Cambron, Michael R. Williamson. . . . (Jul/Aug) 58
Magnetic Resonance Imaging of Radiographically Occult Bony Trauma, Mark Anderson . . . . . (Jul/Aug) 58
Magnetic Resonance Imaging, Positron Emission Tomography, and Single-Proton-Emission Computed Tomography in Epilepsy, Brian W. Chong, David K. Shelton . . . (Jul/Aug) 53
Managing Viral Exposure During Pregnancy, James. D. Goldberg . . . . . (Dec) 376
Measles, see *Pediatric Hospital Admissions for*
Mrs O'Brien's Story (Lessons From the Practice) Gary S. Reiter. . . . . (Jul/Aug) 84
Multidrug-Resistant Tuberculosis—How Far Are We From New York City? Annette T. Nitta. . . . . (Oct) 225
Myocardial Viability (Conferences and Reviews), , Yochai Birnbaum, Robert A. Kloner . . . . . (Dec) 364
Editorial, Robert O. Bonow . . . . . (Dec) 393
Myopia Revisited (Lessons From the Practice), Samuel M. Chen. . . . . (Oct) 254

N

Naltrexone Hydrochloride Use in the Treatment of Alcoholism, Stephen R. Ey. . . . . (Oct) 227
Nursing and Doctoring (Lessons From the Practice), Erika Goldstein. . . . . (Nov) 324

O

Occupational Lead Exposure and Management, James P. Seward . . . . . (Oct) 222
Onychomycosis—New Therapies for an Old Disease, Aditya K. Gupta, Richard K. Scher, Piet De Doncker, Daniel N. Sauder, Neil H. Shear. . . . . (Dec) 349
The Order of the Day? Cheers, Thanks, and Introductions (Editorial), Linda H. Clever . . . . . (Sep) 159

Out-of-Control Snowboarders (Correspondence),
Samuel A. Wise . . . . . (Oct) 252
Response, Terence M. Davidson . . . . . (Oct) 252

P

Parkinson's Disease: A Progress Report (Editorial),
Michael J. Aminoff . . . . . (Oct) 248
Patient Preferences for Management of Localized Prostate Cancer,
Dennis J. Mazur, David H. Hickam . . . . . (Jul/Aug) 26
Parkinson's Disease—Diagnosis and Treatment (Topics in Primary Care Medicine), Don C. Ng . . . . . (Oct) 234
Editorial, Michael J. Aminoff . . . . . (Oct) 248
Pediatric Hospital Admissions for Measles—Lessons From the 1990 Epidemic, Gilberto F. Chavez,
Arthur A. Ellis . . . . . (Jul/Aug) 20
Editorial, Natalie J. Smith, Loring G. Dales,
Stephen H. Waterman . . . . . (Jul/Aug) 80
Percutaneous Core Biopsy of the Breast,
William Brant . . . . . (Jul/Aug) 52
Physicians and Nurse Practitioners—Old Conflicts and New Opportunities (Editorial), Leonard J. Finocchio,
Janet M. Coffman, Catherine M. Dower, Edward H. O'Neil . . . . . (Oct) 246
Physicians—Probationary and Voluntary Treatment Programs Compared, see *Substance-Impaired*
Pneumococcal Pneumonia, see *Sputum Gram's Stain in Community-Acquired*
Pneumoperitoneum, see *Tension*

Poem

Transubstantiation, Catherine Clark-Sayles . . . . . (Oct) 204

Practice Environment for Nurse Practitioners in California—Identifying Barriers, Arlyss L. Anderson, Catherine L. Gilliss,
Laurie Yoder . . . . . (Oct) 209
Editorial, Karen M. Tait, Rebecca J. Patchin . . . . . (Oct) 245
Editorial, Leonard J. Finocchio, Janet M. Coffman,
Catherine M. Dower, Edward H. O'Neil . . . . . (Oct) 246
Predictors of Thyroid Tumor Aggressiveness (Conferences and Reviews), Orlo H. Clark . . . . . (Sep) 131
Editorial, Stefan K.G. Grebe, Ian D. Hay . . . . . (Sep) 156
Prematurity—Steroids for All, Elliott K. Main . . . . . (Dec) 372
Preventing Workers' Hepatitis A, B, C, D, E, and G,
Bruce N. Leistikow . . . . . (Sep) 139
A Primer for Clinicians on Mushroom Poisoning in the West (Editorial), C. Wright Pinson, Anne L. Bradley . . . . (Nov) 318
Probationary and Voluntary Treatment Programs Compared, see *Substance-Impaired Physicians*
Prognosis and Treatment of Burns (Conferences and Reviews),
Roberta Mann, David Heimbach . . . . . (Oct) 215
Prognostic Factors and Management in Thyroid Cancer—Consensus or Controversy? (Editorial), Stefan K.G. Grebe,
Ian D. Hay . . . . . (Sep) 156
Progress in Treatments for Substance-Impaired Physicians (Editorial), James H. Shore . . . . . (Jul/Aug) 81
Prophylaxis Against Opportunistic Infections in Patients Infected With the Human Immunodeficiency Virus (Topics in Primary Care Medicine), Laura W. Cheever, Richard E. Chaisson,
Joel E. Gallant . . . . . (Jul/Aug) 67
Propylthiouracil-Induced Hepatotoxicity (Alerts, Notices, and Case Reports), James T. Hardee, Angela L.Barnett,
Abdul Thannoun, Bijan Eghtesad, Donald Wheeler,
M. Mazen Jamal . . . . . (Sep) 144
Prostate Cancer, see *Patient Preferences for Management of Localized*

R

Radiology, *see Epitomes*
Radiation Synovectomy, Erno J. Gyetvai,
Charles W. Sutter . . . . . (Nov) 301
Radiodosimetry in Nuclear Medicine,
Jerrold T. Bushberg . . . . . (Nov) 301
Radiosurgery, David A. Larson, Michael W.
McDermott . . . . . (Jul/Aug) 59
Relations (Lessons From the Practice),
Nathaniel H. Robin . . . . . (Nov) 326
Role of Lung Scanning in Patients With Pulmonary Embolism,
Fred Mishkin . . . . . (Nov) 303
Ruptured Sinus of Valsalva Aneurysm in a Patient With Autosomal Dominant Polycystic Kidney Disease (Alerts, Notices, and Case Reports), Robert F. Sprung, Renzo M. Cataldo, Martin C. Gregory, Melinda L. Marks, David A. Bull;
Sheldon E. Litwin . . . . . (Dec) 379

S

Salmonella, see *Epidemic* Salmonella enteritidis *Infection in Los Angeles County, California*
Scintimammography—A New Tool for Breast Cancer Diagnosis,
Ira J. Khalkhali, Linda Diggles . . . . . (Nov) 302
The Search for Viable Myocardium (Editorial),
Robert O. Bonow . . . . . (Dec) 393
Selective Deafness (Lessons From the Practice),
Simon Auster . . . . . (Sep) 164
Serious Mushroom Poisonings in California Requiring Hospital Admission, 1990 through 1994, Jeffrey Jacobs,
Julie Von Behren, Richard Kreutzer . . . . . (Nov) 283
Editorial, C. Wright Pinson, Anne L. Bradley . . . . . (Nov) 318
Sir William Macewen's Visit to California as the First Lane Medical Lecturer, Thomas M. Keller . . . . . (Nov) 279
Smoking Cessation—New Challenges and Opportunities,
Bruce N. Leistikow . . . . . (Oct) 226
Spiral Computed Tomography and Magnetic Resonance Imaging in the Detection of Pulmonary Emboli, Mark Baldeck,
Loren Ketai . . . . . (Jul/Aug) 57
Spiral and Ultrafast Computed Tomography for Noninvasive Cardiac Imaging in Children, Sjirk J. Westra . . . . . (Jul/Aug) 55
Spondylosis, see *Cervical*
Spontaneous Group B Streptococcal Meningitis in a Patient With Cirrhosis (Alerts, Notices, and Case Reports),
Bruce Y. Tung, Kris V. Kowdley . . . . . (Oct) 229
Sputum Gram's Stain in Community-Acquired Pneumococcal Pneumonia—A Meta-analysis, William W. Reed, Gregory S. Byrd, Robert H. Gates Jr, Robin S. Howard, Michael J. Weaver . . . . . (Oct) 197
Substance-Impaired Physicians—Probationary and Voluntary Treatment Programs Compared, Heidi D. Nelson,
Annette M. Matthews, Donald E. Girard,
Joseph D. Bloom . . . . . (Jul/Aug) 31
Editorial, James H. Shore . . . . . (Jul/Aug) 81
Surveillance of Traumatic Brain Injuries in Utah, David J. Thurman, Lew Jeppson, Cindy L. Burnett, Denise E. Beaudoin, Marguerite M. Rheinberger, Joseph E. Sniezek . . . . . (Oct) 192
Syphilis, see *Evaluation of Cerebrospinal Fluid in Southeast Asian Refugees With Reactive Serologic Tests for*

T

Tension Pneumoperitoneum, Stephanie Y. Chan, Carl M. Kirsch
William A. Jensen, John Sherck . . . . . (Jul/Aug) 61

Topics in Primary Care Medicine

Action Plans in Asthma Management—Why, When, and How?
Susan Janson . . . . . (Sep) 149
Editorial, Robert E. Dales . . . . . (Sep) 157
Approach to Patients With Hirsutism,
Roland Sakiyama . . . . . (Dec) 386
Editorial, Sanjay K. Agarwal, Howard L. Judd . . . . (Dec) 392
Current Pharmacologic Treatment of Multiple Sclerosis Symptoms,
Peter-Brian Andersson, Donald E. Goodkin . . . . . (Nov) 313
Editorial, Lauren B. Krupp . . . . . (Nov) 320
Parkinson's Disease—Diagnosis and Treatment,

Don C. Ng . . . . . (Oct) 234
Editorial, Michael J. Aminoff . . . . . (Oct) 248
Prophylaxis Against Opportunistic Infections in Patients Infected With the Human Immunodeficiency Virus, Laura W. Cheever, Richard E. Chaisson, Joel E. Gallant. . . . . (Jul/Aug) 67

Torture and War Trauma Survivors in Primary Care Practice, Harvey M. Weinstein, Laura Dansky, Vincent Iacopino. . . . . (Sep) 112
Trends in California Homicide, 1970 to 1993, Lawrence D. Chu, Susan B. Sorenson . . . . . (Sep) 119

U

Use of Bone Mineral Measurements in the Management of Osteoporosis, John M. Vogel. . . . . (Nov) 304
Use of Nucleic Acid in the Diagnosis and Management of Tuberculosis Amplification Tests, Jody Meador, Douglas Moore, Penny Weismuller. . . . . (Sep) 140

V

Venlafaxine Hydrochloride and Chronic Pain (Alerts, Notices, and Case Reports), Kirk Taylor, Michael C. Rowbotham . . . . . (Sep) 147
Violence in America (Correspondence), David C. Stolinsky . . . . . (Dec) 397
Response, Susan B. Sorenson, Lawrence D. Chu . . (Dec) 398

W

What We See Most, We Understand Least (Editorial), Sanjay K. Agarwal, Howard L. Judd. . . . . (Dec) 392
Wegener's Granulomatosis Presenting as Dilated Cardiomyopathy John D. Day, Kristin E. Ellison, Ingela Schnittger, Mark G. Perlroth . . . . . (Jul/Aug) 64
Western Impressions of the Hong Kong Health Care System, Charles L. Bennett, Gloria K. Pei, John E. Ultmann. . . . . (Jul/Aug) 37
When Patients Ask About Assisted Suicide—A Viewpoint From Oregon, Melinda A. Lee, Linda Ganzini, Kenneth Brummel-Smith. . . . . (Oct) 205
Editorial, Albert R. Jonsen . . . . . (Oct) 250

In Memoriam

California Medical Association

Andrews, Alan V., Newport Beach. Died Oct 6, 1996. Graduate of University of Southern California School of Medicine, 1954. Dr Andrews was a member of the Orange County Medical Association.

Bailey, Douglas A., Riverside. Died Jan 22, 1996, aged 80. Graduate of Loma Linda University School of Medicine, 1951. Licensed in California in 1952. Dr Bailey was a member of the Riverside County Medical Association.

Coger, Charles W., San Jose. Died Aug 29, 1996, aged 73. Graduate of Wayne University School of Medicine, 1947. Licensed in California in 1953. Dr Coger was a member of the Santa Clara County Medical Association.

Crown, Ronald F., San Diego. Died Oct 10, 1996, aged 60. Graduate of George Washington University School of Medicine, 1962. Dr Crown was a member of the San Diego County Medical Society.

Derey, Kevin, Orinda. Died Aug 21, 1996, aged 38. Graduate of Harvard Medical School, 1985. Licensed in California in 1988. Dr Derey was a member of the Alameda-Contra Costa Medical Society.

Fish, Victor J., Palo Alto. Died Jan 1, 1996, aged 77. Graduate of University of Breslau School of Medicine, 1946. Licensed in California in 1959. Dr Fish was a member of the Santa Clara County Medical Association.

Hamilton, George R., Los Gatos. Died Jul 10, 1995, aged 87. Graduate of University of Chicago Medical School, 1938. Licensed in California in 1956. Dr Hamilton was a member of the Santa Clara County Medical Association.

Hanshaw, Truman R., Fresno. Died Jan 3, 1995, aged 80. Graduate of College of Medical Evangelists, 1944. Licensed in California in 1950. Dr Hanshaw was a member of the Fresno-Madera Medical Society.

Jamison, Ellis T., Fresno/Sanger. Died Jun 1, 1994, aged 79. Graduate of University of California Medical School, 1942. Licensed in California in 1942. Dr Jamison was a member of the Fresno-Madera Medical Society.

Mari, Phadej, Moreno Valley. Died Jul 1996, aged 53. Graduate of Chulalongkorn University, Thailand, 1968. Licensed in California in 1982. Dr Mari was a member of the Riverside County Medical Association.

Milligan, Joseph R., Fullerton. Died Sep 27, 1996, aged 72. Graduate of University of Virginia School of Medicine, 1956. Dr Milligan was a member of the Orange County Medical Society.

Paulson, Frank. Died Jun 15, 1996, aged 91. Graduate of University of Manitoba School of Medicine, 1934. Dr Paulson was a member of the Santa Clara County Medical Association.

Rath, Richard A. Died Jun 16, 1996, aged 42. Graduate of Washington University School of Medicine, 1980. Licensed in California in 1981. Dr Rath was a member of the Alameda-Contra Costa Medical Society.

Rothenberg, Sam, Fresno. Died Dec 20, 1994, aged 73. Graduate of University of Colorado School of Medicine, 1947. Licensed in California in 1948. Dr Rothenberg was a member of the Fresno-Madera Medical Society.

Rubenstein, Martin, Oakland. Died Nov 11, 1996, aged 70. Graduate of University of Chicago Medical School, 1954. Licensed in California in 1954. Dr Rubenstein was a member of the Alameda-Contra Costa Medical Society.

Seibert, Warren, Napa. Died Nov 8, 1996, aged 63. Graduate of Washington University Medical School, 1957. Dr Seibert was a member of the Napa County Medical Society.

Sterling, Allen F., San Bernardino. Died Oct 6, 1996, aged 83. Graduate of State University of Iowa School of Medicine, 1935. Licensed in California in 1942. Dr Sterling was a member of the San Bernardino County Medical Society.

Winchester, William W., San Jose. Died Jul 20, 1996, aged 83. Graduate of Rush Medical College, 1946. Licensed in California in 1952. Dr Winchester was a member of the Santa Clara County Medical Association.

Wong, Louise May, Woodland. Died Oct 22, 1996, aged 47. Graduate of University of California, Davis School of Medicine, 1974. Dr Wong was a member of the Yolo County Medical Society.

Young, John E., Fresno. Died Sep 9, 1996, aged 87. Graduate of University of California School of Medicine, 1935. Licensed in California in 1937. Dr Young was a member of the Fresno-Madera Medical Society.

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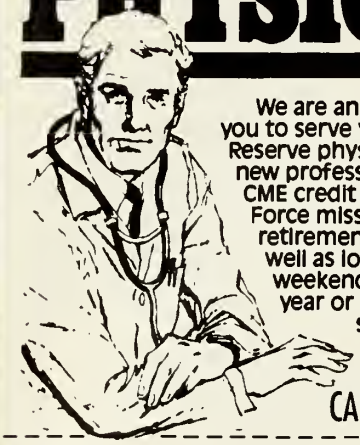

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SCOTT & WHITE 348

SMITHKLINE BEECHAM
Augmentin . . . . . 2nd Cover, 333

THE WESTERN JOURNAL OF MEDICINE
Coming in the January Issue 337
WJM Subscription Order Form 339
Special Issues Catalog 341
www.wjmed.com 412

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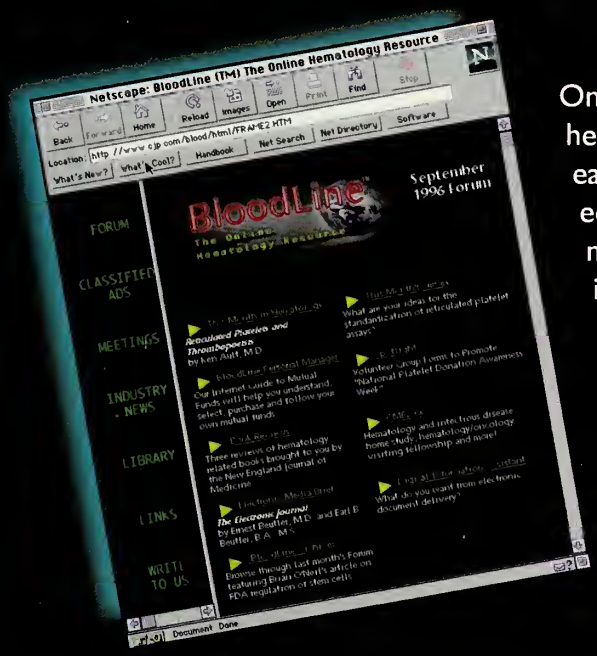

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